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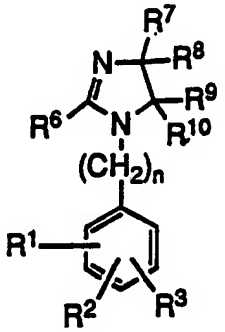

(I)

(57) Abstract

Novel imidazolinone derivatives of formula (I), which are useful as angiotensin II antagonists, are disclosed.

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TITLE

ANGIOTENSIN II RECEPTOR BLOCKING IMIDAZOLINONE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Application Serial Number 07/747,023, filed August 19, 1991.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel substituted imidazolinone derivatives. The invention also relates to pharmaceutical compositions containing the novel imidazolinone derivatives and pharmaceutical methods using them, alone and in conjugation with other drugs.

The compounds of this invention inhibit the action of the hormone angiotensin II (AII) and are useful therefore in alleviating angiotensin induced hypertension. The enzyme renin acts on a blood plasma α2-globulin, angiotensinogen, to produce angiotensin I, which is then converted by ACE to AII. The latter substance is a powerful vasopressor agent which has been implicated as a causative agent for producing high blood pressure in various mammalian species, such as the rat, dog, and man. The compounds of this invention inhibit the action of AII at its receptors on target cells and thus prevent the increase in blood pressure produced by this hormone-receptor interaction. By administering a compound of this invention to a species of mammal with

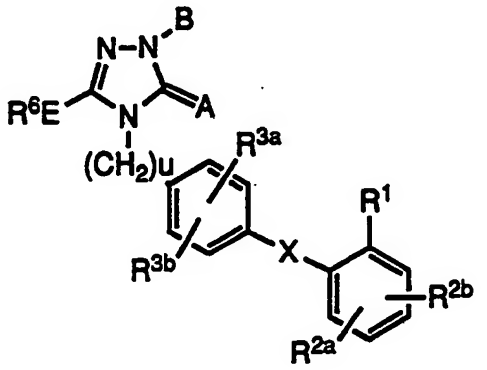
hypertension due to AII, the blood pressure is reduced. The compounds of this invention are also useful for the treatment of congestive heart failure. Administration of a compound of this invention with a diuretic such as furosemide or hydrochlorothiazide, either as a stepwise combined therapy (diuretic first) or as a physical mixture, enhances the antihypertensive effect of the compound. Administration of a compound of this invention with a NSAID can prevent renal failure which sometimes results from administration of a NSAID.

Several peptide analogs of AII are known to inhibit the effects of this hormone by competitively blocking the receptors, but their experimental and clinical applications have been limited by the partial agonist activity and lack of oral absorption (M. Antonaccio, *Clin. Exp. Hypertens.*, **1982**, *A4*, 27-46; D. H. P. Streeten and G. H. Anderson, Jr., Handbook of Hypertension, Clinical Pharmacology of Antihypertensive Drugs, ed., A. E. Doyle, Vol. 5, pages 246-271, Elsevier Science Publisher, Amsterdam, The Netherlands, 1984).

Several non-peptide antagonists of AII have been disclosed. These compounds are covered by U.S. Patents 4,207,324; 4,340,598; 4,576,958; 4,582,847; and 4,880,804; in European Patent Applications 028,834; 245,637; 253,310; and 291,969; and in articles by A. T. Chiu, et al. (*Eur. J. Pharm. Exp. Therap.*, **1988**, *157*, 13-21) and by P. C. Wong, et al. (*J. Pharm. Exp. Therap*, **1988**, *247*, 1-7). All of the U.S. Patents, European Patent Applications 028,834 and 253,310 and the two articles disclose substituted imidazole compounds which are generally bonded through a lower alkyl bridge to a substituted phenyl. European Patent Application 245,637 discloses derivatives of 4,5,6,7-tetrahydro-2H-imidazo[4,5-c]pyridine-6-carboxylic acid and analogs -

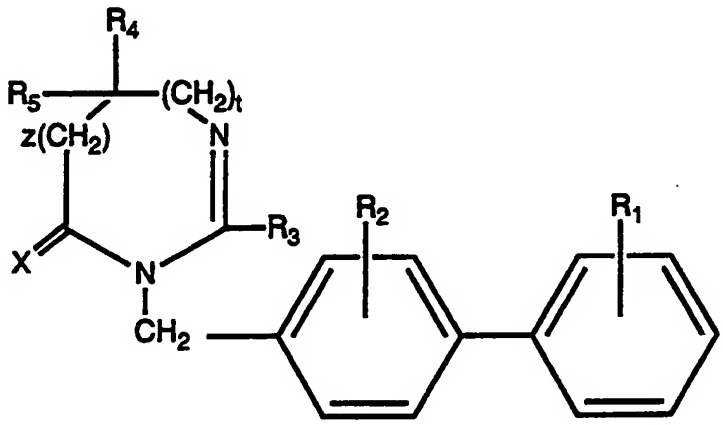
thereof as antihypertensive agents, specifically Ca^{2+} channel blockers.

L. Chang et al., in EP 0 412 594 A (filed July 23, 1990) disclose substituted triazolinones, triazolinethiones, and triazolinimines of the formula:



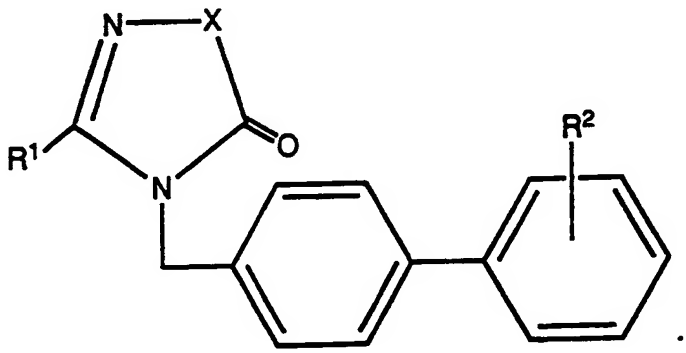
These are claimed to be antagonists of AII which are useful for treating hypertension, congestive heart failure (CHF), and elevated intraocular pressure.

C. Bernhart et al., in WO 91/14679 (published October 3, 1991) disclose heterocyclic N-substituted derivatives of the formula



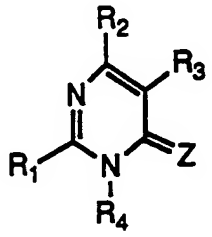
These compounds are disclosed to be antagonists of AII which are useful for treating cardiovascular disorders such as hypertension.

F. Ostermeyer et al., in EP 475,898 (published March 18, 1992) disclose heterocyclic N-substituted derivatives of formula



These compounds are disclosed to be antagonists of AII which are useful for treating cardiovascular disorders such as hypertension.

P. Herold and P. Bühlmayer in EP 0 407 342 A2 disclose substituted pyrimidinones, pyrimidinethiones, and pyrimidinimines of the formula:



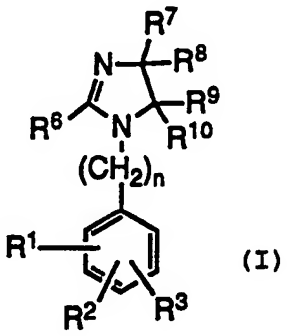
These are claimed to be antagonists of AII which are useful for treating hypertension.

E. Allen, et al. in EP 0 419 048 A (filed August 21, 1990) disclose a similar series of pyrimidinones which are claimed to be antagonists of AII

useful for the treatment of CHF and elevated intraocular pressure.

SUMMARY OF THE INVENTION

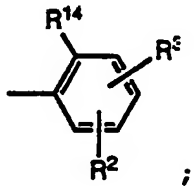
The present invention provides novel angiotensin II receptor antagonists of formula (I), pharmaceutical compositions containing compounds of formula (I) and therapeutic methods using them



(I)

wherein:

R^1 is other than in the ortho position and is:



;

R^2 is

(a) H,

(b) halo (F, Cl, Br, I),

(c) C_1-C_4 alkyl,

(d) C_1-C_4 alkoxy,

(e) C_1-C_4 acyloxy,

(f) C_1-C_4 alkylthio,

(g) C_1-C_4 alkylsulfinyl,

(h) C_1-C_4 alkylsulfonyl,

(i) hydroxy (C_1-C_4) alkyl,

(j) aryl (C_1-C_4) alkyl,
(k) $-CO_2H$,
(l) $-CN$,
(m) tetrazol-5-yl,
(n) $-CONHOR^{13}$,
(o) $-SO_2NHR^{23}$,
(p) $-NH_2$,
(q) C_1-C_4 alkylamino,
(r) C_1-C_4 dialkylamino,
(s) $-NHSO_2R^{24}$,
(t) $-NO_2$,
(u) furyl,
(v) aryl,

wherein aryl is phenyl optionally substituted with one or two substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-CF_3$, C_1-C_4 alkylthio, $-OH$, $-NH_2$, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, $-CN$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2$-benzyl;

R^3 is
(a) H,
(b) halo,
(c) C_1-C_4 alkyl,
(d) C_1-C_4 alkoxy,
(e) C_1-C_4 alkoxyalkyl;

R^4 is
(a) $-CN$,
(b) $-NO_2$,
(c) $-CO_2R^{11}$;

R^5 is
(a) H,
(b) C_1-C_6 alkyl,
(c) C_3-C_6 cycloalkyl,
(d) C_2-C_4 alkenyl,

(e) C_2-C_4 alkynyl;

R^6 is

(a) C_1-C_{10} alkyl,

(b) C_3-C_8 alkenyl,

(c) C_3-C_8 alkynyl,

(d) C_3-C_8 cycloalkyl,

(e) C_4-C_8 cycloalkenyl,

(f) C_4-C_{10} cycloalkylalkyl,

(g) C_5-C_{10} cycloalkylalkenyl,

(h) C_5-C_{10} cycloalkylalkynyl,

(i) $-(CH_2)_sZ^2(CH_2)_mR^5$,

(j) phenyl, optionally substituted with 1-2 substituents selected from the group of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, amino, hydroxy and benzyloxy;

(k) benzyl, optionally substituted on the phenyl ring with 1-2 substituents selected from the group of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy or $-NO_2$;

R^7, R^8, R^9, and R^{10} are independently chosen from

(a) H,

(b) C_1-C_8 alkyl unsubstituted or substituted by one or more halogen

(c) C_3-C_6 cycloalkyl

(d) NO_2,

(e) CN,

(f) $CONR^{15}R^{16}$,

(g) CO_2R^{17},

(h) OR^{18},

(i) $(CH_2)_nCONR^{15}R^{16}$ where n is 1-4,

(j) $(CH_2)_nCO_2R^{17}$ where n is 1-4,

(k) $(CH_2)_nOR^{18}$ where n is 1-4,

(l) aryl, wherein aryl is as defined above,

(m) CH_2aryl, wherein aryl is as defined above,

R^7 and R^8 taken together can be S, O, NR^{19} or $CR^{11}R^{12}$;

R^9 and R^{10} taken together can be $-(CH_2)_t-$, $-(CH_2)_nX(CH_2)_m-$, or NR^{19};

R^9 and R^{10} taken together can be S or O provided that R^7 and R^8 independently or when taken together are not C_1-C_8 alkyl unsubstituted or C_1-C_8 alkyl substituted with a substituent selected from the group of halogen, C_3-C_6 cycloalkyl, $(CH_2)_nOR^{18}$, aryl, wherein aryl is defined as above or $-(CH_2)_t-$;

R^7 and R^9 can be taken together to form an imide $-CONR^{22}CO-$;

R^7 and R^9 taken together can be $-CH_2NR^{22}CH_2-$, provided that both R^7, R^8 and R^9, R^{10} are not S, O, NR^{19} or $-(CH)_t-$;

(n) (3-indolyl) methyl,

(o) (4-imidazolyl) methyl;

R^{11} and R^{12} are independently

(a) H,

(b) C_1-C_6 alkyl,

(c) C_3-C_6 cycloalkyl,

(d) phenyl,

(e) benzyl,

(f) R^{11} and R^{12} when taken together can be $-CH_nXCH_n-$;

R^{13} is

(a) H,

(b) methyl,

(c) benzyl;

R^{14} is

(a) $-CO_2H$,

(b) $-CH_2CO_2H$,

(c) $-C(CF_3)_2OH$,

(d) $-CONHNHSO_2CF_3$,

(e) $-CONHOR^{13}$,

(f) $-CONHSO_2R^{24}$,

(g) $-CONHSO_2NHR^{23}$,

(h) $-C(OH)R^{23}PO_3H_2$,

(i) $-NHCOCF_3$,

(j) $-NHCONHSO_2R^{24}$,

(k) $-NHPO_3H_2$,

(l) $-NHSO_2R^{24}$,

(m) $-NHSO_2NHCOR^{24}$,

(n) $-OPO_3H_2$,

(o) $-OSO_3H$,

(p) $-PO(OH)R^{23}$,

(q) $-PO_3H_2$,

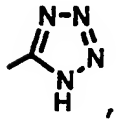
(r) $-SO_3H$,

(s) $-SO_2NHR^{23}$,

(t) $-SO_2NHCOR^{24}$,

(u) $-SO_2NHCONHR^{23}$,

(v)



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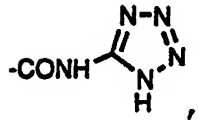

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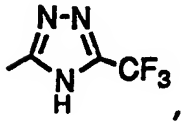

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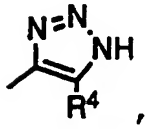

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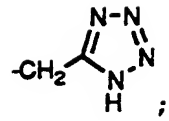
(z)  ;

R^{15} and R^{16} are independently

(a) H,

(b) C_1-C_6 alkyl,

(c) aryl, wherein aryl is as defined above,

(d) aryl (C_1-C_4) alkyl, wherein aryl is as defined above;

R^{15} and R^{16} when taken together can constitute a

(a) piperidine ring,

(b) morpholine ring,

(c) piperazine ring, optionally N-substituted with C_1-C_6 alkyl, phenyl or benzyl;

R^{17} is

(a) H,

(b) C_1-C_6 alkyl,

(c) phenyl,

(d) benzyl;

R^{18} is

(a) H,

(b) C_1-C_6 alkyl,

(c) phenyl,

(d) benzyl;

R^{19} is

(a) H,

(b) OR^{18},

(c) C_1-C_6 alkyl,

(d) aryl,

(e) C_1-C_6 alkyl aryl, wherein aryl is as defined above,

(f) $NR^{20}R^{21}$;

R^{20} and R^{21} are independently

(a) H,

(b) C_1-C_6 alkyl,

(c) phenyl,

(d) benzyl,

R^{20} and R^{21} taken togther can constitute a

(a) piperidine ring,

(b) morpholine ring,

(c) piperazine ring, optionally N-substituted with C_1-C_6 alkyl, phenyl or benzyl;

R^{22} is

(a) H,

(b) C_1-C_6 alkyl,

(c) benzyl;

R^{23} is

(a) H,

(b) C_1-C_5 alkyl,

(c) aryl,

(d) $-CH_2$-aryl, where aryl is defined as above,

(e) heteroaryl;

wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted 5- or 6-membered aromatic ring which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N, and S and wherein the substituents are members selected from the group consisting of -OH, -SH, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CF_3$, halo, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CO_2$-benzyl, $-NH_2$, C_1-C_4 alkylamino, or C_1-C_4 dialkylamino;

R^{24} is

(a) aryl, where aryl is as defined above,

(b) C_3-C_7 cycloalkyl,

(c) C_1-C_4 perfluoroalkyl,

(d) C_1-C_4 alkyl optionally substituted with a substituent selected from the group consisting of aryl

as defined above, heteroaryl as defined above, -OH, -SH, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, $-CF_3$, halo, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CO_2$-benzyl, $-NH_2$, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, or $-PO_3H_2$;

(e) heteroaryl where heteroacryl is as defined above;

X is

(a) S,

(b) O,

(c) $-NR^{22}-$;

Z is

(a) -O-,

(b) -S-,

(c) $-NR^{11}-$;

m is 1 to 5;

n is 1 to 4;

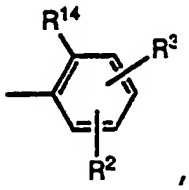
s is 0 to 5;

t is 2 to 5;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of this invention are those of formula (I) wherein

R^1 is in the para position and is



,

R^6 is

(a) C_1-C_{10} alkyl, unsubstituted or substituted with one or more halogen

(b) C_3-C_{10} alkenyl,

(c) C_3-C_{10} alkynyl,

(d) C_3-C_8 cycloalkyl,

(e) phenyl, optionally substituted with 1-2 substituents selected from the group of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, amino, hydroxy and benzyloxy;

(f) benzyl, optionally substituted on the phenyl ring with one or two substitutents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy and $-NO_2$;

R^7, R^8, R^9, R^{10} are independently

(a) H,

(b) C_1-C_8 alkyl unsubstituted or substituted by one or more halogen,

(c) C_3-C_6 cycloalkyl

(d) aryl, wherein aryl is as defined above;

R^7 and R^8 taken together can be S, O, NR^{19} or $CR^{11}R^{12}$;

R^9 and R^{10} taken together can be $-(CH_2)_t-$, $-(CH_2)_nX(CH_2)_m$ or NR^{19}, provided that R^9 and R^{10} are not taken together to form NR^{19} or $-(CH_2)_t-$, when R^7 and R^8 are taken together to form S, O, NR^{19};

R^9 and R^{10} taken together can be S or O provided that R^7 and R^8 independently or when taken together are not C_1-C_8 alkyl unsubstituted or C_1-C_8 alkyl substituted with a substituent selected from the group of halogen, C_3-C_6 cycloalkyl, $(CH_2)_nOR^{18}$, aryl, wherein aryl is defined as above or $-(CH_2)_t-$;

R^{14} is

(a) $-CO_2H$,

(b) $-CONHSO_2R^{24}$,

(c) $-NHCONHSO_2R^{24}$,

(d) $-NHSO_2R^{24}$,

(e) $-NHSO_2NHCOR^{24}$,

(f) $-PO_3H_2$,

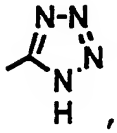
(g) $-SO_3H$,

(h) $-SO_2NHR^{23}$,

(i) $-SO_2NHCOR^{24}$,

(j) $-SO_2NHCONHR^{23}$,

(k)



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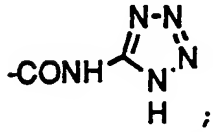
(l)



;

or a pharmaceutically acceptable salt thereof.

Still more preferred are compounds of the above preferred scope formula (I) wherein

R^2 is

(a) H,

(b) halo,

(c) C_1-C_4 alkyl,

(d) C_1-C_4 alkoxy;

R^6 is

(a) C_1-C_7 alkyl,

(b) C_3-C_4 alkenyl,

(c) C_3-C_4 alkynyl;

(d) phenyl, optionally substituted with 1-2 substituents selected from the group of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, amino, hydroxy and benzyloxy;

R^{14} is

(a) $-CO_2H$,

(b) $-CONHSO_2R^{24}$,

(c) $-NHCONHSO_2R^{24}$,

(d) $-NHSO_2R^{24}$,

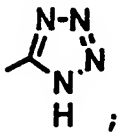
(e) $-NHSO_2NHCOR^{24}$,

(f) $-SO_2NHR^{23}$,

(g) $-SO_2NHCOR^{24}$,

(h) $-SO_2NHCONHR^{23}$,

(i)

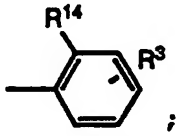


;

or a pharmaceutically acceptable salt thereof.

Most preferred due to their activity as angiotensin II antagonists are compounds of the more preferred scope wherein

R^1 is



;

or a pharmaceutically acceptable salt thereof.

Illustrative of the most preferred compounds of the invention are the following:

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-butyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-butenyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-ditrifluoromethyl-2-propyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dicyclopropyl-2-propyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-butenyl-1-[(2'-(N-((phenylsulfonyl)carboxamido)biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(trifluoromethanesulfonylamido)biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(N-benzoylsulfonamido)biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(N-(4-chloro)benzoylsulfonamido) biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-diazaspiro-((4.5))-deca-3-ene-2-propyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 3,5-Dihydro-5-(1-phenylethylidene)-2-propyl-3-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(N-hexanoylsulfonamido)biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(N-trifluoroacetylsulfonamido)biphen-4-yl)methyl]-4H-imidazol-4-one

Pharmaceutically suitable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in Remington's Pharmaceutical Sciences, 17th Edition, page 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity, and solubility. Preferred salts of this invention for reasons cited above include potassium, sodium, calcium, and ammonium salts.

Detailed Description

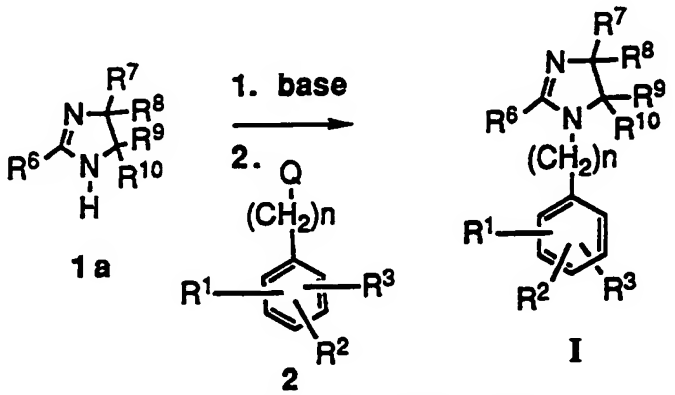
Synthesis

The compounds of formula (I) may be prepared using the reactions and techniques described in this section. The reactions are performed in solvent suitable to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the imidazole and other portions of the molecule must be consistent with the chemical transformations proposed. This will frequently necessitate judgment as to the order of synthetic steps, protecting groups required, deprotection conditions and activation of a benzylic position to enable attachment to nitrogen on the imidazole nucleus. Throughout the following section, not all compounds of formula (I)

falling into a given class may necessarily be prepared by all the methods described for that class. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods described must then be used. The compounds of this application that have a chiral center may be resolved into the pure or partially pure optical isomers by any of the appropriate procedures known to those skilled in the art.

The compounds of formula (I) can be prepared by alkylating the alkali-metal salt of the imidazoline **1a** using appropriately protected benzyl halide, mesylate (OMs), or tosylate (OTs) derivatives **2** as shown in Scheme 1

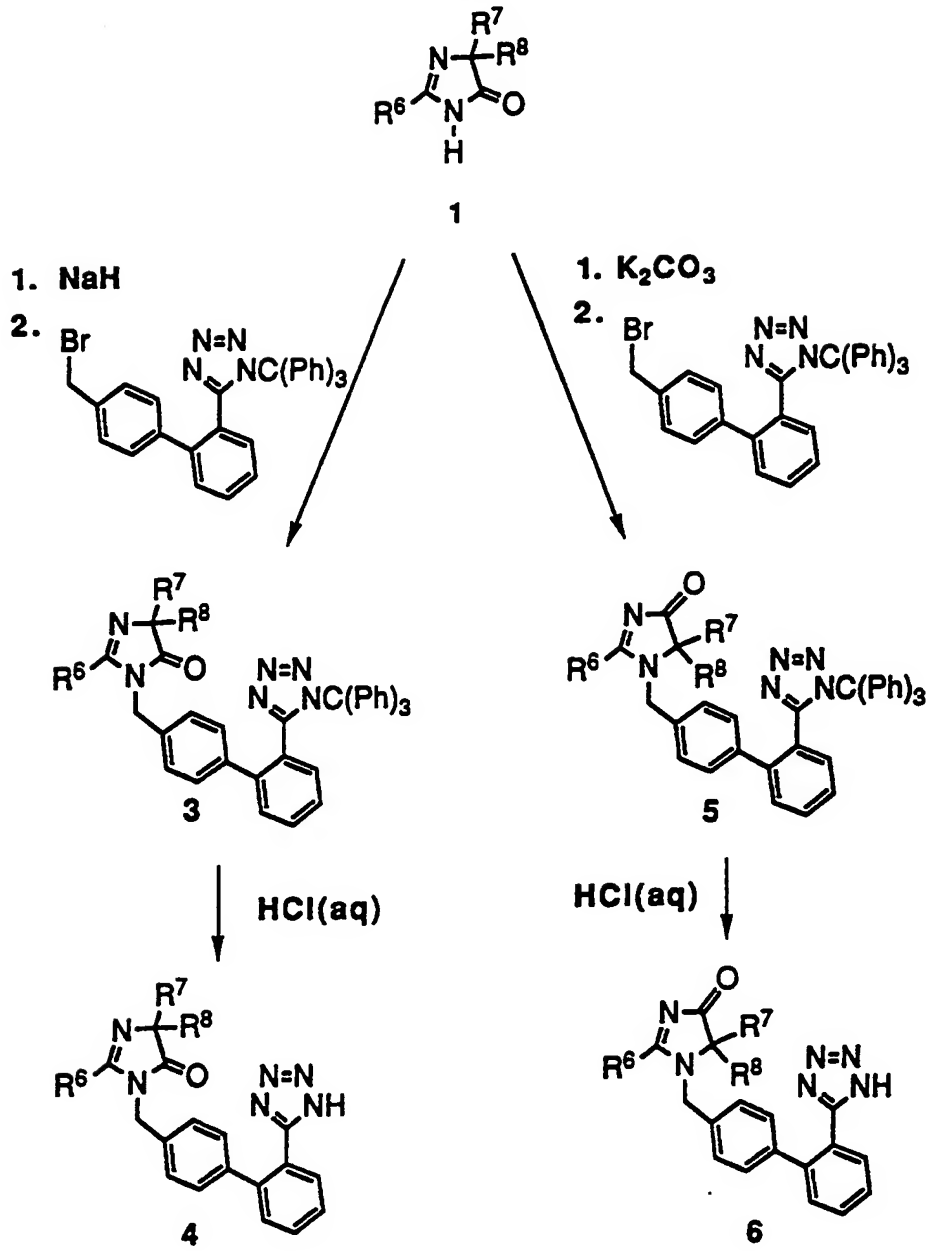
SCHEME 1



Depending on the base, the alkylation may occur selectively on N^1 or N^3. For example, when R^1 is 4-[2'-

(N-triphenylmethyl) tetrazolyl phenyl], R^2 and R^3 are H, R^9 and R^{10} taken together are oxygen, the use of sodium hydride onto the requisite imidazolinone **1** gives compounds of formula **3**. Treatment of **3** with 10% aqueous hydrochloric acid and tetrahydrofuran for a few hours to overnight removes the trityl group from the tetrazole to give the imidazolinone derivative of formula **4**. The structure of of compound **4** has been confirmed by X-ray crystallographic analysis. When potassium carbonate is used as a base, the regioisomer of formula **5** is obtained (Scheme 2). These isomers possess distinct physical and biological properties.

SCHEME 2

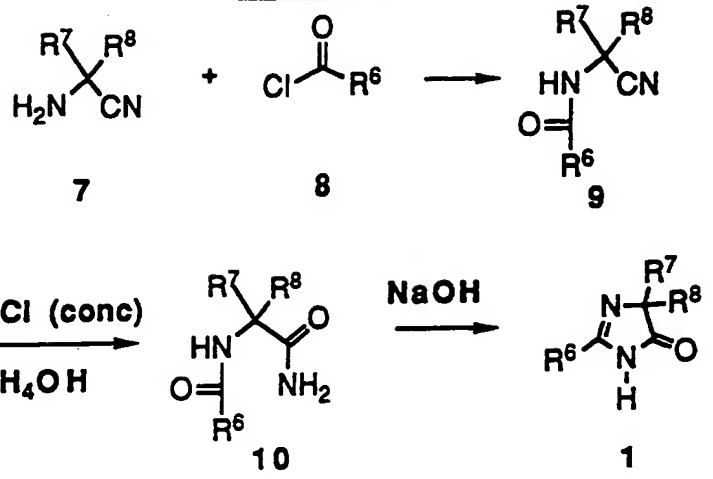


In those cases where the alkylation produces a mixture of the two regioisomers, they can be separated and purified using conventional separation techniques such as chromatography or crystallization. In those cases where separation of regioisomers is difficult by conventional techniques, the mixture can be transformed into suitable derivatives that can be separated by usual separation methods.

The benzyl halides of formula **2** can be prepared as described in European Patent Applications 324,377; 324,377A2; 400 974; 401 030; 400,835; U.S. 4,820,843 and references therein.

The starting imidazolinones are readily available by any number of standard methods. For example imidazolinone of formula **1** can be prepared as shown in Scheme 3. The amino nitrile **7** is readily obtainable from aldehydes and ketones via the Strecker Synthesis and various modifications thereof (R^7= R^8 = CF_3, Y. V. Zeifman, N. P. Gambaryan, I. L. Knunyants, Dokl. Acad. Nauk.S.S.S.R., 153, 1334, 1963). Treatment of the amino nitrile with triethyl amine and one equivalent of the appropriate acyl or aroyl chloride **8** in methylene chloride at room temperature overnight, gives the corresponding amidonitrile **9**. Alternatively, the nitrile can be made following the procedure described in German patent disclosure DE3704100A1. The nitrile can be hydrolyzed to the diamide **10** using standard procedures such as treatment with hydrochloric acid followed by ammonium hydroxide. Treatment of the diamide with 1 N sodium hydroxide as described in E. Mohr, J. Pract. Chem., 81, 49, 1910, gives the imidazolinone **1**.

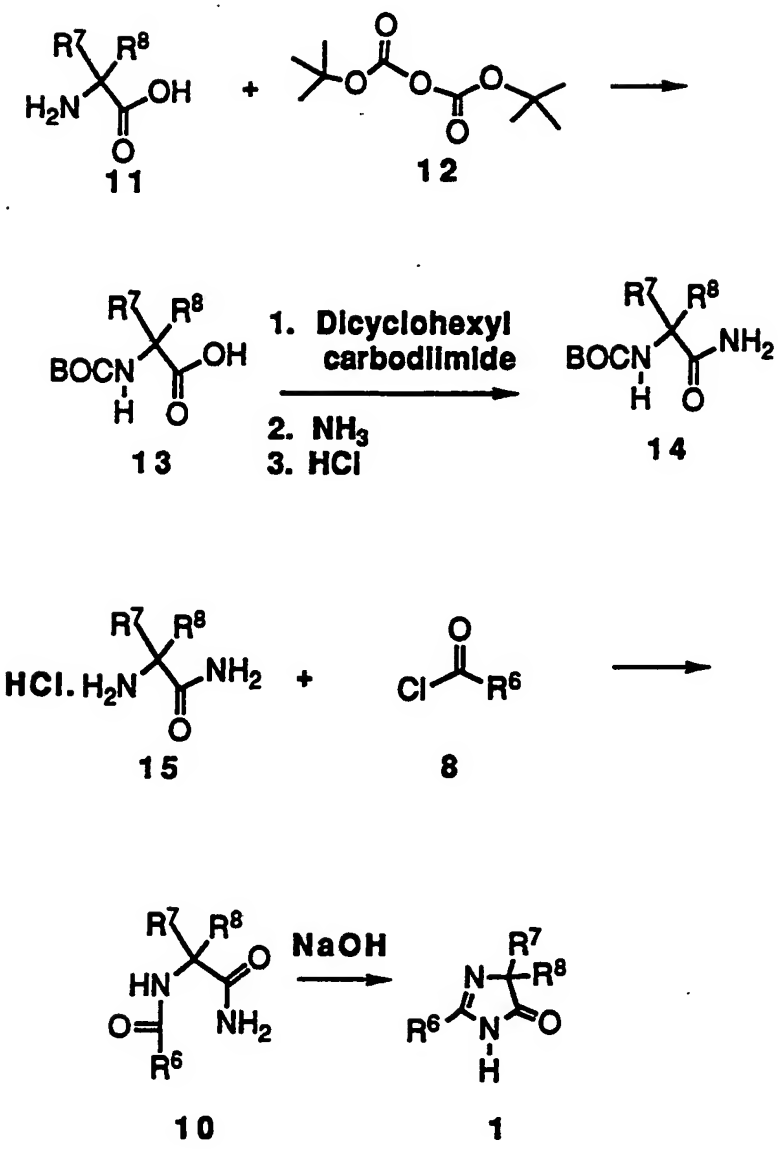
SCHEME 3



7 8 9 10 1

Alternatively, imidazolinones of formula **1** can also be prepared as shown in Scheme 4. Treatment of the amino acid **11** with tert-butyl pyrocarbonate **12** with two or more equivalents of base gives the BOC (tert-butyloxycarbonyl) protected amino acid **13**, M. Bodanszky and A. Bodanszky, The Practice of Peptide Chemistry, 1984. The protected amino amide **14** can be synthesized from the active ester followed by ammonia. Deprotection using HCl gas gives the amino amide hydrochloride **15**. Treatment with two or more equivalents of base and the appropriate acyl or aroyl chloride gives the diamide **10** which can be cyclized by treatment with 1 N sodium hydroxide as described above.

SCHEME 4



Likewise, compound **10** may be obtained by reacting amino acid with the requisite acid chloride by either a Schotten-Baumann procedure, or simply stirring in a solvent such as methylene chloride in the presence of base such as sodium bicarbonate, pyridine or triethyl

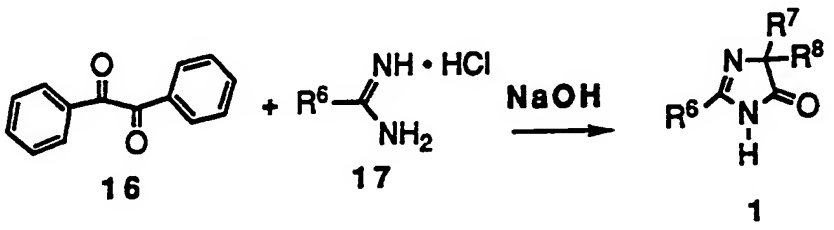
amine followed by coupling reaction with ammonia via a variety of amide or peptide forming reactions such as DCC coupling, azide coupling, mixed anhydride synthesis or any other coupling procedure familiar to one skilled in the art.

The use of 1-amino-1-cycloalkylcarboxylic acids in the above procedure provides the imidazolinone starting materials for the preparation of the spiro-substituted imidazolinones of formula (I).

Imidazolinones of formula **1** can also be prepared following the procedure described in Japanese Patent disclosure JP 58055467.

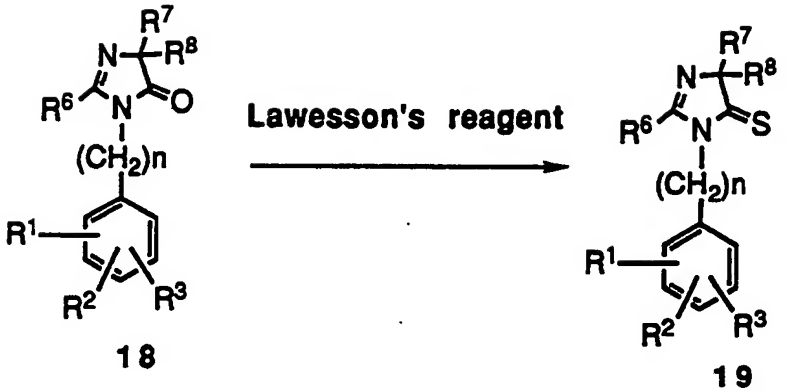
Imidazolinones of formula **1** wherein R^7 and R^8 are both phenyl can be prepared as shown in Scheme 5 by reaction of benzil **16** with alkyl or aryl amidine hydrochloride **17**, A. W. Cox, Org. Syn., 1, 5, R. T. Boere, R. T. Oakley, R. W. Reed, J. Organomet. Chem., 331, 161, 1987, in the presence of base such as 1 N sodium hydroxide, G. Rio and A. Rajon, Bull. Soc. Chim. France, 543, 1958 and references therein.

SCHEME 5



The imidazoline thiones of formula **19** can be prepared by treatment of the requisite alkylated imidazolinone **18** with Lawesson's reagent or phosphorus pentasulfide as described in M. P. Cava and M. I. Levinson, Tetrahedron, 41, 5061, 1985 (Scheme 6).

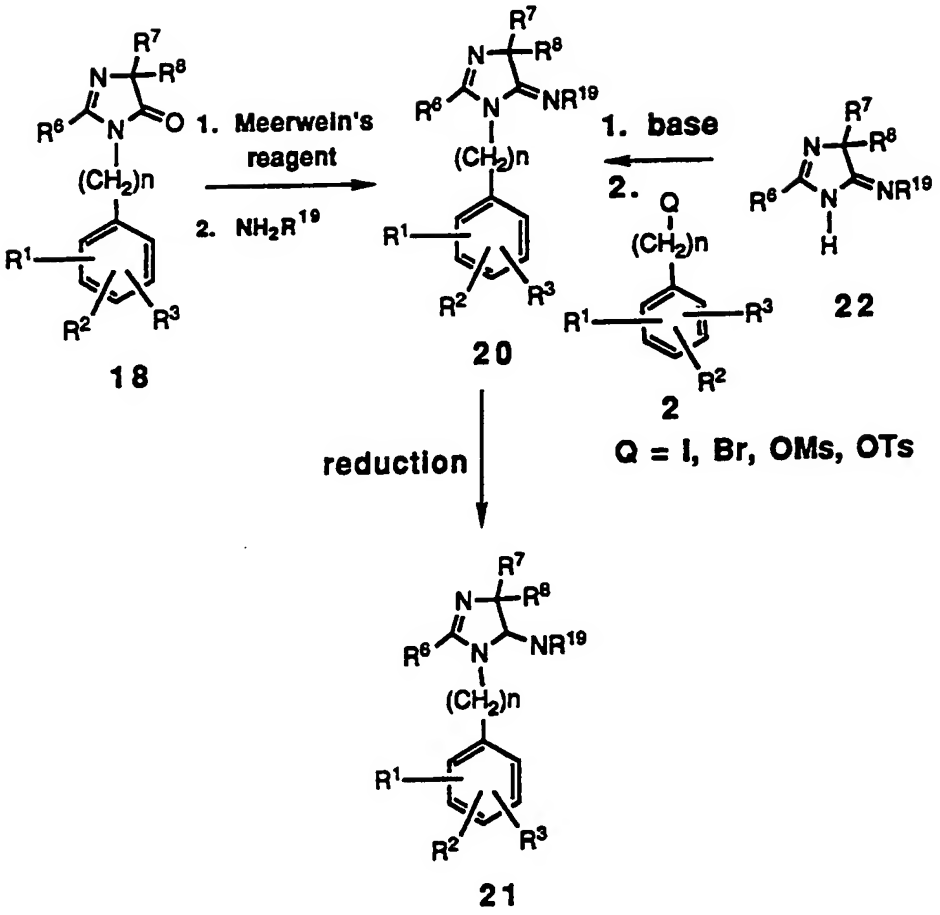
SCHEME 6



18 19

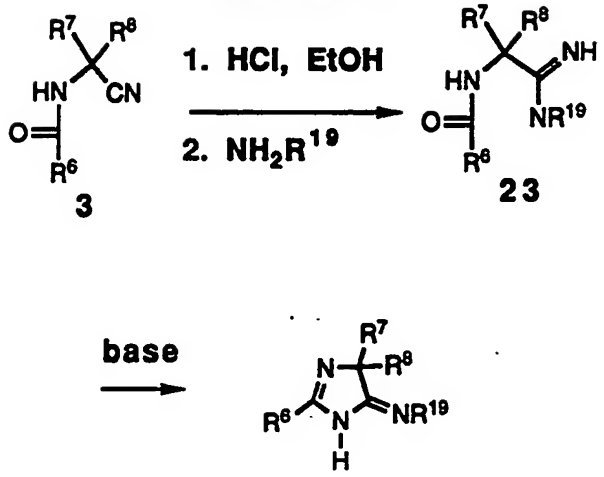
Compounds of formula **20** can be prepared by treatment of the requisite alkylated imidazolinone **18** with Meerwein's reagent, H. Meerwein, Org. Syn., 5, 1080, 1973, in ether followed by treatment with ammonia, alkyl or aryl amines, hydroxyl amines or hydrazines, as shown in Scheme 7. The aminals of formula **21** can be prepared by reducing the requisite imines of formula **20** with lithium aluminum hydride in tetrahydrofuran or sodium borohydride in ethanol for 1 to 24 hours at room temperature to the boiling temperature of solvent. Alternatively, compounds of formula **20** can be prepared by alkylating the imines of formula **22** with the requisite benzyl halides **2**.

SCHEME 7



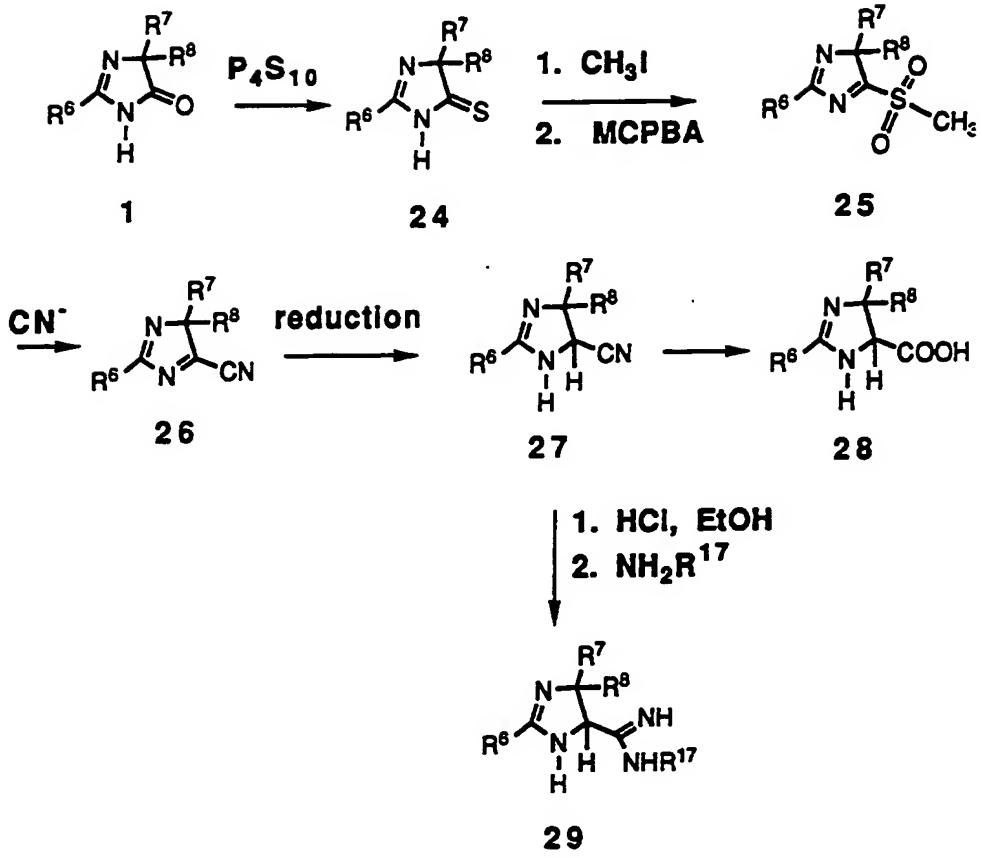
The imines of formula **22** can be prepared from base catalyzed cyclization reaction of the amido amidine **23** which was prepared by treatment of the amido nitrile of formula **9** with anhydrous HCl in ethanol followed by ammonia (Scheme 8).

SCHEME 8



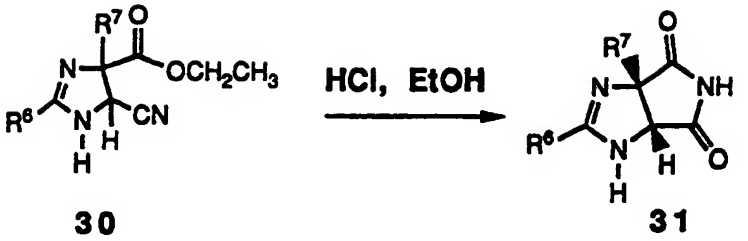
As shown in Scheme 9, the imidazoline thione of formula **24** wherein R^7 or R^8 cannot be hydrogen can be prepared by treating the requisite imidazolinone **1** with Lawesson's reagent or phosphorus pentasulfide as described in M. P. Cava and M. I. Levinson, Tetrahedron, 41, 5061, 1985. Alkylation using base such as sodium hydride followed by alkyl halide such as methyl iodide followed by oxidation with meta-chloroperbenzoic acid (MCPBA) gives the (methyl sulfonyl)imidazole **25** which can be subjected to nucleophilic displacement reaction with nucleophiles such as cyanide to give cyanoimidazoles **26**. The cyanoimidazoles can be selectively reduced to give the cyanoimidazoline **27**. The nitrile group can be further elaborated into other functional groups such as carboxylic acid **28**, amidine **29** by methods familiar to one skilled in the art.

SCHEME 9

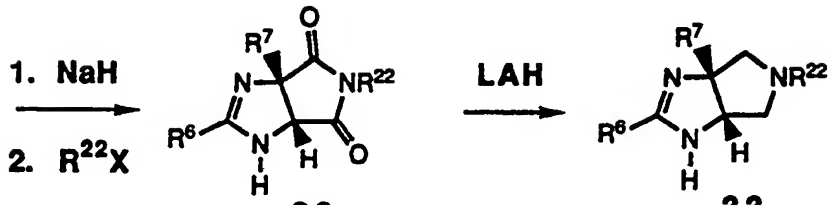


The cyanoimidazoline **30** can be hydrolyzed and cyclized using standard procedure such as treatment with hydrochloric acid and ethanol to form the cyclic imide (**31**, Scheme 10). Alkylation using base such as sodium hydride followed by alkyl halide gives the cyclic imide derivative **32** which can be reduced with reducing agent such as diisobutylaluminum hydride (DIBAL-H) or lithium aluminum hydride to give compound **33**.

SCHEME 10



30 31

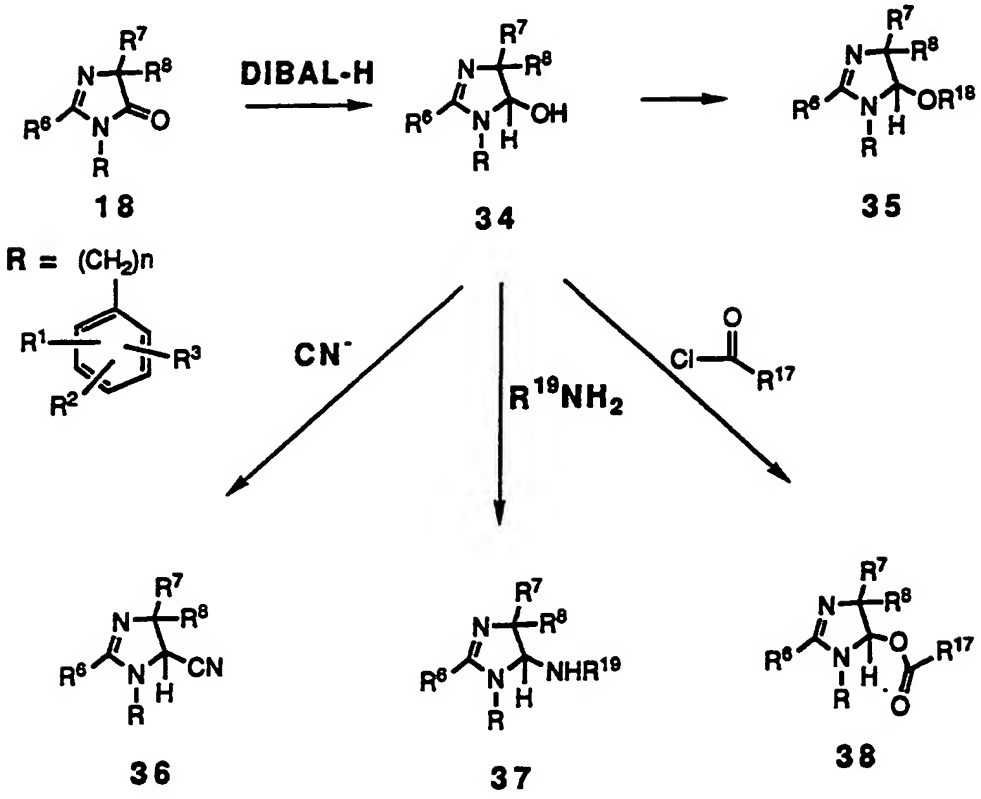


32 33

As shown in Scheme 11, the hydroxy imidazoline **34** can be prepared by reduction of the requisite imidazolinone wherein R^7 and/or R^8 cannot be hydrogen with reducing agents such as DIBAL-H. The hydroxyl group may be readily converted to the ethers **35** by a variety of procedures such as treatment with potassium t-butoxide, sodium hydride or the like in solvent such as dimethyl formamide followed by treatment with alkyl halide, tosylate or mesylate at room temperature for 1-24 hours. The hydroxyl group wherein R^7 and/or R^8 is not polyfluoro or perfluoroalkyl may be acylated to give esters of formula **38**. Acylation can be achieved with 1-3 equivalents of an acyl halide or an anhydride in a solvent such as diethyl ether, methylene chloride in the presence of base such as triethyl amine or pyridine. The hydroxy imidazoline can be heated or treated with formic acid to form the acyliminium ion which can be treated with nucleophiles such as cyanide to form

cyanoimidazoline **36** or amines to form aminoimidazoline **37**.

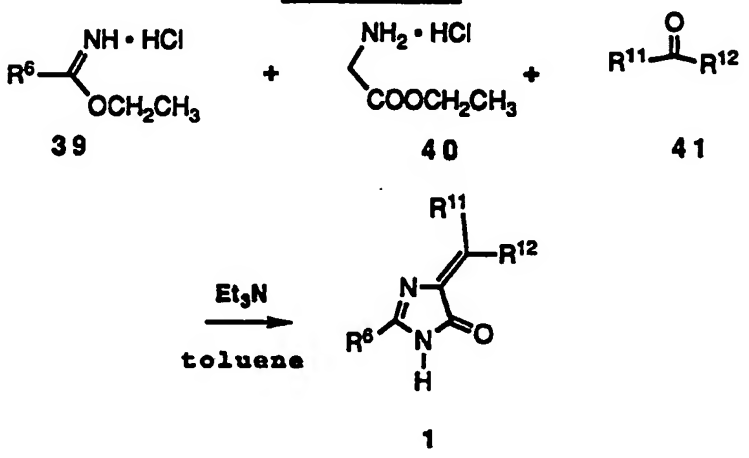
SCHEME 11



Imidazolinones of formula **1** wherein R^7 and R^8 taken together are $CR^{11}R^{12}$ can be prepared as described by J. Lamboy, J. Am. Chem. Soc., 76, 133, 1954, A. Jain and A. K. Mukerjee, J. Indian Chem. Soc., 65, 141, 1988, H. Lehr et al., J. Org. Chem., 75, 3640, 1953. Scheme 12 shows the reaction of alkyl or aryl imidate **39** with glycine ethyl ester hydrochloride **40** and a ketone **41** in refluxing toluene and tertiary base such as triethyl amine to give the desired imidazolinone. The imidate

hydrochloride salt can be prepared by following Mc Elvain, J. Am. Chem. Soc., 64, 1825, 1942. Treatment with base such as K_2CO_3 in organic solvent such as methylene chloride gives the free base.

SCHEME 12



The compounds of this invention and their preparation can be understood further by the following examples which do not constitute a limitation of the invention. In these examples, unless otherwise indicated, all temperatures are in degrees centigrade and parts and percentages are by weight.

EXAMPLE 1

Preparation of 1,5-Dihydro-5,5-dimethyl-2-propyl-1-[(2'-(1H- tetrazol-5-yl)(1,1'-biphenyl)-4-yl) methyl]-4H-imidazol-4-one

PART A: Preparation of 2-N-Butyramido-isobutyronitrile

Butyryl chloride (23.0 g, 0.22 mol) was added dropwise to a cooled mixture of 2-amino-isobutyronitrile (16.8 g, 0.20 mol) and triethyl amine (25 g, 0.25 mol) in methylene chloride (300 ml). The mixture was stirred for 3 hours at room temperature after which it was poured into 1N HCl (50 ml). The organic layer was washed with 1N HCl (2x50 ml), 1N NaOH (2x50 ml), dried ($MgSO_4$) and concentrated. The residue was triturated with hexane to give a pale yellow solid (18.2 g, 59%), m.p. 57.9-58.4; MS m/e 155.2 (M^++H)
NMR ($CDCl_3$/TMS) δ 0.96 (t, 3H, J=7Hz, CH_3), 1.69 (m, 2H, CH_2), 1.70(s,6H, 2 CH_3), 2.18 (t, 2H, J=7Hz, CH_2), 5.74 (s, 1H, NH)

PART B: Preparation of 2-N-Butyramido-isobutylamide

2-N-Butyramido isobutyronitrile (6.0 g, 38.9 mmol) was dissolved in concentrated hydrochloric acid (10 ml) at 0°C. Cold water (50 ml) was added immediately followed by treatment with concentrated ammonium hydroxide to pH 5-6. The mixture was extracted successively with methylene chloride. The organic layer was combined and concentrated to give white solid (5.4 g, 82%). M.P. 155.9-157.4, M.S. m/e 173.2 (M^++H)
NMR ($CDCl_3$/TMS) δ 0.95 (t, 3H, J=7Hz, CH_3), 1.59 (s,6H, 2 CH_3), 1.66 (m, 2H, CH_2), 2.17 (t, 2H, J=7Hz, CH_2), 5.57 (s, 1H, NH), 6.10 (s, 1H, NH), 6.60 (s, 1H, NH)

PART C: Preparation of 2-Propyl-4,4-dimethyl-1H-imidazol-5(4H)-one

2-N-Butyramido-isobutylamide (5.4 g, 31.4 mmol) was dissolved in 1N sodium hydroxide (40 ml) and heated at 80°C for 30 minutes. The mixture was cooled to room temperature and extracted successively with ethyl acetate. The combined organic layer was concentrated and the residue was chromatographed over silica gel eluting with ethyl acetate to give 2.1 g white solid: m.p. 66.5-68.5 M.S. m/e 155.2 (M^++H)
NMR ($CDCl_3$/TMS) δ 1.01 (t, 3H, J=7Hz, CH_3), 1.34 (s, 6H, 2 CH_3), 1.73 (m, 2H, CH_2), 2.44 (t, 2H, J=7Hz, CH_2)

PART D: Preparation of 1,5-Dihydro-5,5-dimethyl-2-propyl-1-[(2'-(triphenyl methyl tetrazol-5-yl)(1,1'-biphenyl)-4-yl) methyl]-4H-imidazol-4-one

A mixture of potassium carbonate (500 mg,3.7 mmol), 2-propyl-4-4-dimethyl-1H-imidazol-5(4H)-one (0.6 g, 3.9 mmol), and 4'-bromomethyl-2-(triphenyl methyl tetrazol-5-yl) biphenyl (1.08 g, 1.9 mmol) in dimethyl formamide (5 ml) was allowed to stir at room temperature overnight. The mixture was chromatographed over silica gel eluting with ethyl acetate-hexane to give 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(triphenyl methyl tetrazol-5-yl)(1,1'-biphenyl)-4-yl) methyl]-4H-imidazol-4-one (70 mg, 14%) M.S. m/e 631.5 (M^++H)
NMR ($CDCl_3$/TMS) δ 0.88 (t, 3H, J=7Hz, CH_3), 1.38 (s,6H, 2 CH_3), 1.67 (m, 2H, CH_2), 2.21 (t, 2H, J=7Hz, CH_2), 4.56 (s, 2H, CH_2), 6.92 (d, J=7Hz, 8H, H_{arom}), 7.11 (d, J=7Hz, 2H, H_{arom}), 7.24-7.38 (m, 10H, H_{arom}), 7.47 (m, 2H, H_{arom}), 7.92 (m, 1H, H_{arom})

PART E: Preparation of 1,5-Dihydro-5,5-dimethyl-2-propyl-1-[(2'-(1H- tetrazol-5-yl)(1,1'-biphenyl)-4-yl) methyl]-4H-imidazol-4-one

1,5-Dihydro-5,5-dimethyl-2-propyl-1-[(2'-(triphenyl methyl tetrazol-5-yl)(1,1'-biphenyl)-4-yl) methyl]-4H-imidazol-4-one (60 mg, 0.1 mmol) in tetrahyrofuran (5 ml) and 10% hydrochloric acid (3 ml) was allowed to stir at room temperature overnight. The reaction mixture was treated with 50% sodium hydroxide to pH 8, concentrated and cooled in ice bath. The precipitate was filtered and the aqueous solution was adjusted to pH 3 using concentrated hydrochloric acid to give white solid which was recrystalized from ethyl acetate hexane to give amorphous solid (23 mg, 62%).
M.P. 127.5-129.9 M.S. m/e 389.2 (M^++H)
NMR ($CDCl_3$/TMS) δ 0.98 (t, 3H, J=7Hz, CH_3), 1.50 (s, 6H, 2 CH_3), 1.76 (m, 2H, CH_2), 2.64 (t, 2H, J=7Hz, CH_2), 4.77 (s, 2H, CH_2), 7.14 (s, 4H, H_{arom}), 7.41-7.58 (m, 3H, H_{arom}), 7.90 (m, 1H, H_{arom})

EXAMPLE 2

3,5-Dihydro-5-(1-phenylethylidene)-2-propyl-3-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

PART A: Preparation of 2-propyl-4-(1-phenylethyledene)-1H-imidazol-5(4H)-one

To a mixture of acetophenone (1.2 ml, 0.01 mol), glycine ethyl ester hydrochloride (2.80 g, 0.02 mol) and ethyl butyrimidate (3.0 g, 0,02 mol) in 100 ml toluene was

added triethyl amine (7.0 ml, 5 eq.). The mixture was heated at 80°C under N_2 for 12 hours. The solvent was removed and the residue was partitioned between CH_2CL_2 and water. The layers were separated. The aqueous layer was extrated with CH_2CL_2. The combined organic layer was washed with brine, concentrated and chromatographed over silica gel eluting with 1:1 hexane:ethyl acetate, to give 0.35 g of the z isomer and 0.08 g of the E isomer. M.S. m/e 229 (M^++H)

Z isomer, NMR ($CDCl_3$/TMS) δ 1.01 (t, 3H, CH_3), 1.76 (m, 2H, CH_2), 2.53 (t, 2H, CH_2), 2.73 (s, 3H, CH_3), 7.39 (m, 3H, H_{arom}), 7.78 (d, 2H, H_{arom}), 9.30 (S, 1H, NH).

E isomer, NMR ($CDCl_3$/TMS) δ 1.01 (t, 3H, CH_3), 1.72 (m, 2H, CH_2), 2.48 (t, 2H, CH_2), 2.50 (s, 3H, CH_3), 7.40 (m, 5H, H_{arom}), 9.0 0 (S, 1H, NH).

PART B: Preparation of 3,5-dihydro-5-(1-phenylethylidene)-2-propyl-3-[(2'-(triphenylmethyltetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

Sodium hydride (0.15 g, 1.5 eq., 50% suspention in oil) was added to .2-propyl-4-(1-phenylethyledene)-1H-imidazol-5(4H)-one (0.47 g, 2.1 mmol) in dimethyl formamide (20 ml). The mixture was allowed to stir at room temperature for 15 minutes. 4'-Bromomethyl-2-(triphenyl methyl tetrazol-5-yl) biphenyl (1.50 g, 1.28 eq.) was added and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was poured into water and extracted with ether. The organic layer was washed successively with water and saturated sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel eluting with ethyl acetate-hexane 1:4 to give

3,5-dihydro-5-(1-phenylethyledene)-2-propyl-3-[(2'-(triphenyl methyl tetrazol-5-yl)(1,1'-biphenyl)-4-yl) methyl]-4H-imidazol-4-one (0.22 g, light yellow foam). NMR ($CDCl_3$/TMS) δ 0.89 (t, 3H, CH_3), 1.60 (m, 2H, CH_2), 2.31 (m, 2H, CH_2), 2.80 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 6.91 (d, 6H, H_{arom}), 6.99 (d, 2H, H_{arom}), 7.10 (d, 2H, H_{arom}), 7.20-7.50 (m, 15H, H_{arom}), 7.80 (d, 2H, H_{arom}), 7.92 (d, 1H, H_{arom}).

PART C: Preparation of 3,5-dihydro-5-(1-phenylethylidene)-2-propyl-3-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

3,5-dihydro-5-(1-phenylethylidene)-2-propyl-3-[(2'-(triphenylmethyltetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one (0,17 g) in tetrahyrofuran (20 ml) and 10% hydrochloric acid (5 ml) was allowed to stir at room temperature for 3.5 hr. The reaction mixture was treated with 50% sodium hydroxide to pH 8, concentrated and cooled in ice bath. The precipitate was filtered and the aqueous solution was adjusted to pH 4-5 using concentrated hydrochloric acid to give white solid which was washed with cold water and dried to give yellow solid (80 mg) as a mixture of the Z and E isomers (8:2). M.S. m/e 463 (M^++H)
NMR ($CDCl_3$/TMS) δ 0.98 (t, 3H, CH_3), 1.67 (m, 2H, CH_2), 2.39 (t, 2H, CH_2), 2.76 (s, 3H, CH_3), 4.80 (s, 2H, CH_2), 7.04-7.20 (m, 4H, H_{arom}), 7.42-7.61 (m, 2H, H_{arom}), 7.63 (d, 2H, H_{arom}), 7.99 (d, 1H, H_{arom})

EXAMPLE 3

3,5-Dihydro-5-(diphenylmethylene)-2-propyl-3-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

A mixture of potassium carbonate (83 mg,2 eq.), 2-propyl-4-(diphenylmethylene)-1H-imidazol-5(4H)-one (90 mg, 0.3 mmol), and 4'-bromomethyl-2-(triphenyl methyl tetrazol-5-yl) biphenyl (0.21 g, 1.2 eq.) in dimethyl formamide (10 ml) was allowed to stir at room temperature for 2 days. The solvent was *in vacuo*, the residue was dissolved in CH_2CL_2 and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude mixture was chromatographed over silica gel eluting with ethyl acetate-hexane (1:4) to give 3,5-dihydro-5-(diphenylmethylene)-2-propyl-3-[(2'-(triphenyl methyl tetrazol-5-yl)(1,1'-biphenyl)-4-yl) methyl]-4H-imidazol-4-one (100 mg). M.S. m/e 767 (M^++H)

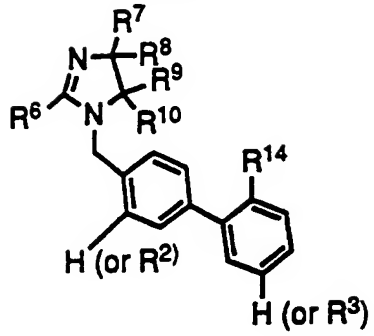
NMR ($CDCl_3$/TMS) δ 0.90 (m, 3H, CH_3), 1.65 (m, 2H, CH_2), 2.38 (m, 2H, CH_2), 4.62 (s, 2H, CH_2), 6.88-7.50 (m, 30H, H_{arom}), 7.61 (m, 2H, H_{arom}), 7.90 (d, 1H, H_{arom})

The above compound was detritylated following the procedure described in Example 2C, to give 61 mg of the desired product.M.S. m/e 524 (M^++H)

NMR ($CDCl_3$/TMS) δ 1.01 (t, 3H, CH_3), 1.78 (m, 2H, CH_2), 2.49 (t, 2H, CH_2), 4.75 (s, 2H, CH_2), 7.12-7.41 (m, 15H, H_{arom}), 7.58 (m, 2H, H_{arom}), 8.10 (d, 1H, H_{arom})

Compounds 1-230 in Table 1 can be prepared by the procedures described in Examples 1,2,3 employing the appropriately substituted imidazolinones and benzyl halides.

TABLE 1



EX.	R^6	R^7	R^8	R^9	R^{10}	R^{14}	M.S. (M^++H)
1	n-Pr	O		CH_3	CH_3	1H-Tetrazol-5-yl	389
2	n-Pr	$C(C_6H_5)(CH_3)$		O		1H-Tetrazol-5-yl	463
3	n-Pr	$C(C_6H_5)_2$		O		1H-Tetrazol-5-yl	525
4	n-Pr	O		CH_3	CH_3	$-CONHSO_2C_6H_5$	
5	n-Pr	O		CH_3	CH_3	$-SO_2NHCOC_6H_5$	
6	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$	
7	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(cy-C_3H_5)$	
8	n-Pr	O		CH_3	CH_3	$-SO_2NHCOCH_2C_6H_5$	
9	n-Pr	O		CH_3	CH_3	$-CO_2H$	
10	n-Pr	O		CH_3	CH_3	$-CH_2CO_2H$	
11	n-Pr	O		CH_3	CH_3	$-C(CF_3)_2OH$	
12	n-Pr	O		CH_3	CH_3	$-CONHNHSO_2CF_3$	
13	n-Pr	O		CH_3	CH_3	$-SO_2NHCOC_6H_5$ (R^2=CH_3)	
14	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)	
15	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(cy-C_3H_5)$ (R^2=CH_3)	
16	n-Pr	O		CH_3	CH_3	$-CONHOCH_3$ (R^2=CH_3)	
17	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-Bu)$ (R^2=CH_3)	
18	n-Pr	O		CH_3	CH_3	$-SO_2NHCOCH_2C_6H_5$ (R^2=CH_3)	
19	n-Pr	O		CH_3	CH_3	$-SO_2NHCONH(n-Bu)$ (R^2=CH_3)	
20	n-Pr	O		CH_3	CH_3	$-NHSO_2NHCO(n-Bu)$ (R^2=CH_3)	

Ex.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
21	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(i-C_4H_9)$ (R^2=CH_3)
22	n-Pr	O		CH_3	CH_3	$-CONHSO_2C_2H_4OH$ (R^2=CH_3)
23	n-Pr	O		CH_3	CH_3	$-CONHSO_2NH(4-ClC_6H_4)$ (R^2=CH_3)
24	n-Pr	O		CH_3	CH_3	$-C(OH)CH_3PO_3H_2$
25	n-Pr	O		CH_3	CH_3	$-SO_2NHCOC_6H_5$ (R^2=Cl)
26	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=Cl)
27	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(cy-C_3H_5)$ (R^2=Cl)
28	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(i-C_5H_{11})$ (R^2=Cl)
29	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-Bu)$ (R^2=Cl)
30	n-Pr	O		CH_3	CH_3	$-SO_2NHCOCH_2C_6H_5$ (R^2=Cl)
31	n-Pr	O		CH_3	CH_3	$-SO_2NHCONH(n-Bu)$ (R^2=Cl)
32	n-Pr	O		CH_3	CH_3	$NHCOCF_3$ (R^2=Cl)
33	n-Pr	O		CH_3	CH_3	$-NHPO_2H$ (R^2=Cl)
34	n-Pr	O		CH_3	CH_3	$-NHCONHSO_2(i-C_5H_{11})$ (R^2=Cl)
35	n-Pr	O		CH_3	CH_3	$-NHSO_2(cy-C_3H_5)$ (R^2=Cl)
36	n-Pr	O		CH_3	CH_3	$-OPO_3H_2$ (R^2=Cl)
37	n-Pr	O		CH_3	CH_3	$-SO_2NHCOC_6H_5$ (R^2=F)

Ex.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
38	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=F)
39	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(cy-C_3H_5)$ (R^2=F)
40	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(i-C_5H_{11})$ (R^2=F)
41	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-Bu)$ (R^2=F)
42	n-Pr	O		CH_3	CH_3	$-SO_2NHCOCH_2C_6H_5$ (R^2=F)
43	n-Pr	O		CH_3	CH_3	$-SO_2NHCONH(n-Bu)$ (R^2=F)
44	n-Pr	O		CH_3	CH_3	$-OSO_3H$ (R^2=F)
45	n-Pr	O		CH_3	CH_3	$-PO(OH)(n-C_5H_{11})$ (R^2=F)
46	n-Pr	O		CH_3	CH_3	$-PO_3H_2$ (R^2=F)
47	n-Pr	O		CH_3	CH_3	$-SO_3H$ (R^2=F)
48	n-Pr	O		CH_3	CH_3	$-SO_2NH(4-C_5NH_4)$ (R^2=F)
49	n-Pr	O		CH_3	CH_3	$-SO_2NHCOC_6H_5$ (R^3=n-Pr)
50	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
51	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(cy-C_3H_5)$ (R^3=n-Pr)
52	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(i-C_5H_{11})$ (R^3=n-Pr)
53	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-Bu)$ (R^3=n-Pr)
54	n-Pr	O		CH_3	CH_3	$-SO_2NHCOCH_2C_6H_5$ (R^3=n-Pr)

EX.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
55	n-Pr	O		CH_3	CH_3	$-SO_2NHCONH(n-Bu)$ (R^3=n-Pr)
56	n-Pr	O		CH_3	CH_3	$-SO_2NH(n-Bu)$ (R^3=n-Pr)
57	n-Pr	O		CH_3	CH_3	$-SO_2NHCONH(n-C_5H_{11})$ (R^3=n-Pr)
58	n-Pr	O		CH_3	CH_3	$-SO_2NHCONH(i-C_5H_{11})$ (R^3=n-Pr)
59	n-Pr	O		CH_3	CH_3	$-SO_2NHCONH(cy-C_3H_5)$ (R^3=n-Pr)
60	n-Pr	O		CH_3	CH_3	$-SO_2NHCONHCH_2C_6H_5$ (R^3=n-Pr)
61	n-Pr	O		CH_3	CH_3	$-SO_2NHCOC_6H_5$ (R^2=Cl, R^3=n-Pr)
62	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=Cl, R^3=n-Pr)
63	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(cy-C_3H_5)$ (R^2=F, R^3=n-Pr)
64	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(i-C_5H_{11})$ (R^2=F, R^3=n-Pr)
65	n-Pr	O		CH_3	CH_3	$-SO_2NHCO(n-Bu)$ (R^2=Cl, R^3=n-Pr)
66	n-Pr	O		CH_3	CH_3	$-SO_2NHCOCH_2C_6H_5$ (R^2=F, R^3=n-Pr)
67	n-Pr	O		CH_3	CH_3	$-NHSO_2NHCO(n-Bu)$ (R^2=Cl, R^3=n-Pr)
68	n-Pr	O		CH_3	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$ (R^2=F, R^3=n-Pr)
69	n-Pr	O		CH_3	CH_3	$-NHSO_2NHCO(i-C_5H_{11})$ (R^2=Cl, R^3=n-Pr)
70	n-Pr	O		CH_3	CH_3	$-NHSO_2NHCO(cy-C_3H_5)$ (R^2=Cl, R^3=n-Pr)

Ex.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
71	n-Pr	O		CH_3	CH_3	$-NHSO_2NHCOCH_2C_6H_5$ (R^2=F, R^3=n-Pr)
72	n-Pr	O		CH_3	CH_3	$-SO_2NHCOCF_3$
73	n-Pr	N		CH_3	CH_3	1H-Tetrazol-5-yl
74	n-Pr	N		CH_3	CH_3	$-SO_2NHCO(4Cl-C_6H_4)$
75	n-Pr	N		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
76	n-Pr	N		CH_3	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
77	n-Pr	S		CH_3	CH_3	1H-Tetrazol-5-yl
78	n-Pr	S		CH_3	CH_3	$-SO_2NHCO(4Cl-C_6H_4)$
79	n-Pr	S		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
70	n-Pr	S		CH_3	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
81	n-Bu	N		CH_3	CH_3	1H-Tetrazol-5-yl
82	n-Bu	S		CH_3	CH_3	1H-Tetrazol-5-yl
83	n-Bu	S		CH_3	CH_3	$-NHSO_2NHCO(n-Bu)$
84	n-Bu	O		CH_3	CH_3	$-CONHSO_2C_6H_5$
85	n-Bu	O		CH_3	CH_3	$-SO_2NHCOC_6H_5$
86	n-Bu	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$
87	n-Bu	O		CH_3	CH_3	$-SO_2NHCO(cy-C_3H_5)$
88	n-Bu	O		CH_3	CH_3	$-SO_2NHCOCH_2Ph$
89	n-Bu	O		CH_3	CH_3	$-NHSO_2NHCO(i-C_4H_9)$
90	n-Bu	O		CH_3	CH_3	$-NHSO_2NHCO(n-Bu)$
91	n-Bu	O		CH_3	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$
92	n-Bu	O		CH_3	CH_3	$-NHSO_2NHCO(cy-C_3H_5)$
93	n-Bu	O		CH_3	CH_3	$-NHSO_2NHCOCH_2Ph$
94	n-Bu	O		CH_3	CH_3	$-SO_2NHCO(4Cl-C_6H_4)$
95	n-Bu	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)

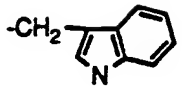
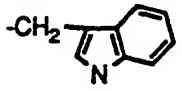
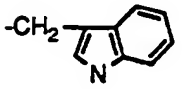
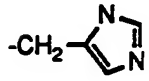
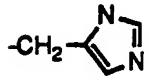
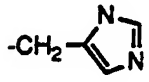
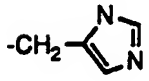
Ex.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
96	n-Bu	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
97	n-Bu	O		CH_3	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
98	n-Bu	O		CH_3	CH_3	$-NHSO_2NHCO$(n-Bu) (R^2=Cl)
99	n-Bu	O		CH_3	CH_3	$-SO_2NHCOCF_3$
100	n-Bu	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=Cl, R^3=n-Pr)
101	n-Bu	O		CH_3	CH_3	$-NHSO_2NHCO(i-C_5H_{11})$ (R^2=F, R^3=n-Pr)
102	n-Bu	O		CH_3	CH_3	$-SO_2NHCONH$(n-Bu) (R^2=Cl)
103	n-Pr	S		C_2H_5	CH_3	$-NHSO_2NHCO$(n-Bu)
104	n-Pr	O		C_2H_5	CH_3	$-CONHSO_2C_6H_5$
105	n-Pr	O		C_2H_5	CH_3	$-SO_2NHCOC_6H_5$
106	n-Pr	O		C_2H_5	CH_3	$-SO_2NHCO(n-C_5H_{11})$
107	n-Pr	O		C_2H_5	CH_3	$-SO_2NHCO(cy-C_3H_5)$
108	n-Pr	O		C_2H_5	CH_3	$-SO_2NHCOCH_2Ph$
109	n-Pr	O		C_2H_5	CH_3	$-NHSO_2NHCO(i-C_4H_9)$
110	n-Pr	O		C_2H_5	CH_3	$-NHSO_2NHCO$(n-Bu)
111	n-Pr	O		C_2H_5	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$
112	n-Bu	O		C_2H_5	CH_3	$-NHSO_2NHCO(cy-C_3H_5)$
113	n-Bu	O		C_2H_5	CH_3	$-NHSO_2NHCOCH_2Ph$
114	n-Bu	O		C_2H_5	CH_3	$-SO_2NHCO(4Cl-C_6H_4)$
115	n-Bu	O		C_2H_5	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
116	n-Bu	O		C_2H_5	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
117	n-Bu	O		C_2H_5	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
118	n-Bu	O		C_2H_5	CH_3	$-NHSO_2NHCO$(n-Bu) (R^2=Cl)
119	n-Bu	O		C_2H_5	CH_3	$-SO_2NHCOCF_3$

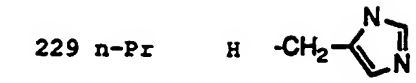
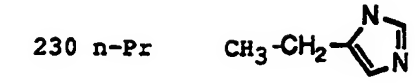
EX.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
120	n-Bu	O		C_2H_5	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=Cl, R^3=n-Pr)
121	n-Bu	O		C_2H_5	CH_3	$-NHSO_2NHCO(i-C_5H_{11})$ (R^2=F, R^3=n-Pr)
122	n-Bu	O		C_2H_5	CH_3	$-SO_2NHCONH(n-Bu)$ (R^2=Cl)
123	n-Pr	O		C_2H_5	C_2H_5	1H-Tetrazol-5-yl
124	n-Pr	O		C_2H_5	C_2H_5	$-CONHSO_2C_6H_5$
125	n-Pr	O		C_2H_5	C_2H_5	$-SO_2NHCOC_6H_5$
126	n-Pr	O		C_2H_5	C_2H_5	$-SO_2NHCO(n-C_5H_{11})$
127	n-Bu	O		C_2H_5	C_2H_5	$-SO_2NHCO(cy-C_3H_5)$
128	n-Pr	O		C_2H_5	C_2H_5	$-SO_2NHCOCH_2Ph$
129	n-Bu	O		CF_3	CF_3	$-NHSO_2NHCO(i-C_4H_9)$
130	n-Bu	O		C_2H_5	C_2H_5	$-NHSO_2NHCO(n-Bu)$
131	n-Pr	O		CF_3	CF3	$-NHSO_2NHCO(n-C_5H_{11})$
132	n-Pr	O		CF_3	CF3	$-NHSO_2NHCO(cy-C_3H_5)$
133	n-Bu	O		CF_3	CF_3	$-NHSO_2NHCOCH_2Ph$
134	n-Bu	O		CF_3	CF3	$-SO_2NHCO(4Cl-C_6H_4)$
135	pF-Ph	O		CF_3	CF3	$-SO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
136	pF-Ph	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
137	pF-Ph	O		CH_3	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
138	Ph	O		CH_3	CH_3	$-NHSO_2NHCO(n-Bu)$ (R^2=Cl)
139	Ph	O		CH_3	CH_3	$-SO_2NHCOCF_3$
140	Ph	O		CH_3	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^2=Cl, R^3=n-Pr)
141	CH_3	O		CH_3	CH_3	$-NHSO_2NHCO(i-C_5H_{11})$ (R^2=F, R^3=n-Pr)
142	CH_3	O		CH_3	CH_3	$-SO_2NHCONH(n-Bu)$ (R^2=Cl)
143	CH_3	O		C_2H_5	CH_3	$-NHSO_2NHCO(n-Bu)$
144	CH_3	O		C_2H_5	C_2H_5	$-CONHSO_2C_6H_5$
145	C_2H_5	O		C_2H_5	C_2H_5	$-SO_2NHCOC_6H_5$

EX.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
146	C_2H_5		O	C_2H_5	CH_3	$-SO_2NHCO(n-C_5H_{11})$
147	C_2H_5		O	C_2H_5	CH_3	$-SO_2NHCO(cy-C_3H_5)$
148	C_2H_5		O	C_2H_5	CH_3	$-SO_2NHCOCH_2Ph$
149	$-CH_3CH_2CH=CH_2$		O	C_2H_5	CH_3	$-NHSO_2NHCO(i-C_4H_9)$
150	$-CH_3CH_2CH=CH_2$		O	CH_3	CH_3	$-NHSO_2NHCO(n-Bu)$
151	$-CH_3CH_2CH=CH_2$		O	CH_3	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$
152	$-CH_3CH_2CH=CH_2$		O	CH_3	CH_3	$-NHSO_2NHCO(cy-C_3H_5)$
153	C_2H_5		O	CH_3	CH_3	$-NHSO_2NHCOCH_2Ph$
154	C_2H_5		O	CH_3	CH_3	$-SO_2NHCO(4Cl-C_6H_4)$
155	C_2H_5		O	C_2H_5	CH_3	$-SO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
156	C_2H_5		O	C_2H_5	CH_3	$-SO_2NHCO(n-C_5H_{11})$ ($R^2=CH_3$)
157	C_2H_5		O	C_2H_5	CH_3	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
158	C_2H_5		O	C_2H_5	CH_3	$-NHSO_2NHCO(n-Bu)$ (R^2=Cl)
159	n-Pr		O	$-(CH_2)_5-$		$-SO_2NHCOCF_3$
160	n-Pr		O	$-(CH_2)_4-$		$-SO_2NHCO(n-C_5H_{11})$ (R^2=Cl, R^3=n-Pr)
161	n-Pr		O	$-(CH_2)_2-$		$-NHSO_2NHCO(i-C_5H_{11})$ (R^2=F, R^3=n-Pr)
162	n-Pr		O	cy-Pr	cy-Pr	$-NHSO_2NHCO(n-Bu)$ ($R^2=CH_3$)
163	n-Pr	$C(C_6H_5)(CH_3)$		S		1H-Tetrazol-5-yl
164	n-Pr	$C(C_6H_5)(CH_3)$		O		$-CONHSO_2C_6H_5$
165	n-Pr	$C(C_6H_5)(CH_3)$		O		$-SO_2NHCOC_6H_5$
166	n-Pr	$C(C_6H_5)(CH_3)$		O		$-SO_2NHCO(n-C_5H_{11})$
167	n-Pr	$C(C_6H_5)(CH_3)$		O		$-SO_2NHCO(cy-C_3H_5)$
168	n-Pr	$C(C_6H_5)(CH_3)$		O		$-SO_2NHCOCH_2Ph$
169	n-Pr	$C(C_6H_5)(CH_3)$		O		$-NHSO_2NHCO(i-C_4H_9)$
170	n-Bu	$C(C_6H_5)(CH_3)$		O		$-NHSO_2NHCO(n-Bu)$

Ex.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
171	n-Pr	$C(C_6H_5)(CH_3)$			O	$-NHSO_2NHCO(n-C_5H_{11})$
172	C_2H_3	$C(C_6H_5)(CH_3)$			O	$-NHSO_2NHCO(cy-C_3H_5)$
173	n-Bu	$C(C_6H_5)(CH_3)$			O	$-NHSO_2NHCOCH_2Ph$
174	Ph	$C(C_6H_5)(CH_3)$			O	$-SO_2NHCO(4Cl-C_6H_4)$
175	pF-Ph	$C(C_6H_5)(CH_3)$			O	$-SO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
176	n-Pr	$C(C_6H_5)(CH_3)$			O	$-SO_2NHCO(n-C_5H_{11})$ ($R^2=CH_3$)
177	n-Pr	$C(C_6H_5)(CH_3)$			O	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
178	n-Pr	$C(C_6H_5)(CH_3)$			O	$-NHSO_2NHCO(n-Bu)$ ($R^2=Cl$)
179	n-Pr	CH_3	CH_3		N	$-SO_2NHCOCF_3$
180	CH_3	CH_3	CH_3		N	$-SO_2NHCO(n-C_5H_{11})$ ($R^2=Cl$, R^3=n-Pr)
181	Ph	CH_3	CH_3		N	$-NHSO_2NHCO(i-C_5H_{11})$ ($R^2=F$, R^3=n-Pr)
182	pF-Ph	CH_3	CH_3		N	$-SO_2NHCONH(n-Bu)$ ($R^2=Cl$)
183	n-Pr	C_2H_5	C_2H_5		N	1H-Tetrazol-5-yl
184	n-Pr	C_2H_5	CH_3		N	$-SO_2NHCO(4Cl-C_6H_4)$
185	n-Pr	CF_3	CF_3		N	$-SO_2NHCO(n-C_5H_{11})$ ($R^2=CH_3$)
186	n-Bu	CH_3	CH_3		N	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
187	n-Pr	CH_3	CH_3		N	1H-Tetrazol-5-yl
188	n-Pr	CF_3	CF_3		N	$-SO_2NHCO(4Cl-C_6H_4)$
189	n-Pr	$-(CH_2)_2-$			N	$-SO_2NHCO(n-C_5H_{11})$ ($R^2=CH_3$)
190	n-Pr	$-(CH_2)_2-$			N	$-NHSO_2NHCO(n-C_5H_{11})$
191	n-Pr	$C(C_6H_5)_2$			S	1H-Tetrazol-5-yl
192	n-Bu	$C(C_6H_5)_2$			S	1H-Tetrazol-5-yl
193	n-Pr	$C(C_6H_5)_2$			N	1H-Tetrazol-5-yl

EX.	R^6	R^7 R^8	R^9	R^{10}	R^{14}
194	n-Pr	$C(C_6H_5)_2$		O	$-CONHSO_2C_6H_5$
195	n-Pr	$C(C_6H_5)_2$		O	$-SO_2NHCOC_6H_5$
196	n-Pr	$C(C_6H_5)_2$		O	$-SO_2NHCO(n-C_5H_{11})$
197	n-Pr	$C(C_6H_5)_2$		O	$-SO_2NHCO(cy-C_3H_5)$
198	n-Pr	$C(C_6H_5)_2$		O	$-SO_2NHCOCH_2Ph$
199	n-Pr	$C(C_6H_5)_2$		O	$-NHSO_2NHCO(i-C_4H_9)$
200	n-Bu	$C(C_6H_5)_2$		O	$-NHSO_2NHCO(n-Bu)$
201	n-Pr	$C(C_6H_5)_2$		O	$-NHSO_2NHCO(n-C_5H_{11})$
202	C_2H_3	$C(C_6H_5)_2$		O	$-NHSO_2NHCO(cy-C_3H_5)$
203	Ph	$C(C_6H_5)_2$		O	$-SO_2NHCO(4Cl-C_6H_4)$
204	pF-Ph	$C(C_6H_5)_2$		O	$-SO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
205	n-Pr	$C(C_6H_5)_2$		O	$-NHSO_2NHCO(n-Bu)$ (R^2=CH_3)
206	n-Pr	$C(C_6H_5)_2$		O	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
207	n-Pr	$C(C_6H_5)_2$		O	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
208	n-Pr	$C(C_6H_5)(CH_3)$		O	$-NHSO_2NHCO(n-Bu)$ (R^2=Cl)
209	n-Bu	$-(CH_2)_3-$		N	$-NHSO_2NHCOCH_2Ph$
210	Ph	$-(CH_2)_4-$		N	$-SO_2NHCO(4Cl-C_6H_4)$
211	pF-Ph	$-(CH_2)_4-$		N	$-SO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
212	n-Pr	$-(CH_2)_4-$		N	$-NHSO_2NHCO(n-Bu)$ (R^2=CH_3)
213	n-Pr	$-(CH_2)_5-$		N	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
214	n-Pr	$-(CH_2)_5-$		N	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)

EX.	R^6	R^7 R^8	R^9	R^{10}	R^{14}
215	n-Bu	$-(CH_2)_4-$		N	$-NHSO_2NHCO$(n-Bu) (R^2=CH_3)
216	n-Pr	CH_3 		O	1H-Tetrazol-5-yl
217	n-Pr	CH_3 		O	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
218	n-Pr	H 		O	1H-Tetrazol-5-yl
219	n-Pr	H 		O	$-SO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
220	n-Pr	H CH_2COOH		O	1H-Tetrazol-5-yl
221	n-Pr	H CH_2COOH		O	$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
222	n-Pr	H CH_2COOH		O	$-SO_2NHCO(cy-C_3H_5)$
223	n-Pr	H CH_2COOH		O	$-NHSO_2NHCO$(n-Bu) (R^2=CH_3)
224	n-Pr	CH_3 CH_2COOH		O	$-NHSO_2NHCO$(n-Bu) (R^2=CH_3)
225	n-Pr	H 		O	1H-Tetrazol-5-yl
226	n-Pr	CH_3 		O	1H-Tetrazol-5-yl
227	n-Pr	H 		O	$-NHSO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)
228	n-Pr	CH_3 		O	$-NHSO_2NHCO(n-C_5H_{11})$ (R^2=CH_3)

EX.	R^6	R^7	R^8	R^9	R^{10}	R^{14}
229	n-Pr	H		O		$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)
230	n-Pr			O		$-NHSO_2NHCO(n-C_5H_{11})$ (R^3=n-Pr)

Utility

Angiotensin II (AII) produces numerous biological responses (e.g., vasoconstriction) through stimulation of its receptors on cell membranes. For the purpose of identifying compounds such as AII antagonists which are capable of interacting with the AII receptor, a ligand-receptor binding assay was utilized for the initial screen. The assay was carried out according to the method described by Chiu, et al., Receptor, 1 33, (1990). In brief, aliquots of a freshly prepared particulate fraction of rat adrenal cortex were incubated with 0.05 nM [^{125}I] AII and varying concentrations of potential AII antagonists in a Tris buffer. After a 1 h incubation the reaction was terminated by addition of cold assay buffer. The bound and free radioactivity were rapidly separated through glass-fiber filters, and the trapped radioactivity was quantitated by scintillation counting. The inhibitory concentration (IC_{50}) of potential AII antagonists which gives 50% displacement of the total specifically bound [^{125}I] AII is presented as a measure of the affinity of such compound for the AII receptor.

Using the assay method described above, the compounds of this invention are found to exhibit an activity of at least IC_{50} <10 micromolar, thereby demonstrating and confirming the activity of these compounds as effective AII antagonists.

The potential antihypertensive effects of the compounds of this invention may be demonstrated by administering the compounds to awake rats made hypertensive by ligation of the left renal artery [Cangiano et al., *J. Pharmacol. Exp. Ther.*, **1979**, *208*, 310]. This procedure increases blood pressure by increasing renin production with consequent elevation of AII levels. Compounds are administered intravenously via a cannula in the jugular vein at 10 mg/kg. Arterial blood pressure is continuously measured directly through a carotid artery cannula and recorded using a pressure transducer and a polygraph. Blood pressure levels after treatment are compared to pretreatment levels to determine the antihypertensive effects of the compounds.

Using the in vivo methodology described above, the compounds of this invention are found to exhibit an activity (intravenous) which is 10 mg/kg or less, and/or an activity (oral) which is 100 mg/kg or less, thereby demonstrating and confirming the utility of these compounds as effective agents in lowering blood pressure.

The compounds of the invention are useful in treating hypertension. They are also of value in the management of acute and chronic congestive heart failure and angina. These compounds may also be expected to be useful in the treatment of primary and secondary hyperaldosteronism; renal diseases such as diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end

stage renal disease, used in renal transplant therapy, and to treat renovascular hypertension, scleroderma, left ventricular dysfunction, systolic and diastolic dysfunction, diabetic retinopathy and in the management of vascular disorders such as migraine, Raynaud's disease, and as prophylaxis to minimize the atherosclerotic process and neointimal hyperplasia following angioplasty or vascular injury and to retard the onset of type II diabetes. The application of the compounds of this invention for these and similar disorders will be apparent to those skilled in the art.

The compounds of this invention are also useful to treat elevated intraocular pressure and to enhance retinal blood flow and can be administered to patients in need of such treatment with typical pharmaceutical formulations such as tablets, capsules, injectables and the like as well as topical ocular formulations in the form of solutions, ointments, inserts, gels and the like. Pharmaceutical formulations prepared to treat intraocular pressure would typically contain about 0.1% to 15% by weight, preferably 0.5% to 2% by weight, of a compound of this invention. For this use, the compounds of this invention may also be used in combination with other medications for the treatment of glaucoma including choline esterase inhibitors such as physostigmine salicylate or demecarium bromide, parasympathominetic agents such as pilocarpine nitrate, β-adrenergic antagonists such as timolol maleate, adrenergic agonists such as epinephrine and carbonic anhydrase inhibitors such as MK-507.

In the management of hypertension and the clinical conditions noted above, the compounds of this invention may be utilized with a pharmaceutical carrier in compositions such as tablets, capsules or elixirs for

oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diet that is being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize, the dosage range will generally be about 1 to 1000 mg per patient per day which can be administered in single or multiple doses. Preferably, the dosage range will be about 5 to 500 mg per patient per day; more preferably about 5 to 300 mg per patient per day.

The compounds of this invention can also be administered in combination with other antihypertensives and/or diuretics. For example, the compounds of this invention can be given in combination with diuretics such as hydrochlorothiazide, chlorothiazide, chlorthalidone, methylclothiazide, furosemide, ethacrynic acid, triamterene, amiloride spironolactone and atriopeptin; calcium channel blockers, such as diltiazem, felodipine, nifedipine, amlodipine, nimodipine, isradipine, nitrendipine and verapamil; β-adrenergic antagonists such as timolol, atenolol, metoprolol, propanolol, nadolol and pindolol; angiotensin converting enzyme inhibitors such as enalapril, lisinopril, captopril, ramipril, quinapril and zofenopril; renin inhibitors such as A-69729, FK 906 and FK 744; α-adrenergic antagonists such as prazosin, doxazosin, and terazosin; sympatholytic agents such as

methyldopa, clonidine and guanabenz; atriopeptidase inhibitors (alone or with ANP) such as UK-79300; serotonin antagonists such as ketanserin; A_2-adrenosine receptor agonists such as CGS 22492C; potassium channel agonists such as pinacidil and cromakalim; and various other antihypertensive drugs including reserpine, minoxidil, guanethidine, hydralazinc hydrochloride and sodium nitroprusside as well as combinations of the above-named drugs. Combinations useful in the management of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and phosphodiesterase inhibitors including amrinone and milrinone.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly. To illustrate these combinations, one of the angiotensin II antagonists of this invention effective clinically in the 5-500 milligrams per day range can be effectively combined at levels at the 1.0-500 milligrams per day range with the following compounds at the indicated per day dose range; hydrochlorothiazide (6-100 mg), chlorothiazide (125-500 mg), ethacrynic acid (5-200 mg), amiloride (5-20 mg), furosemide (5-80 mg), propranolol (10-480 mg), timolol maleate (1-20 mg), methyldopa (125-2000 mg), felodipine (1-20 mg), nifedipine (5-120 mg), nitrendipine (5-60 mg), and diltiazem (30-540 mg). In addition, triple drug combinations of hydrochlorothiazide (5-100 mg) plus amiloride (5-20 mg) plus angiotensin II antagonists of this invention (1-500 mg) or hydrochlorothiazide (5-100 mg) plus timolol maleate (5-60 mg) plus an angiotensin

II antagonists of this invention (1-500 mg) or hydrochlorothiazide (5-200 mg) and nifedipine (5-60 mg) plus an angiotensin II antagonist of this invention (1-500 mg) are effective combinations to control blood pressure in hypertensive patients. Naturally, these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably

contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is

100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

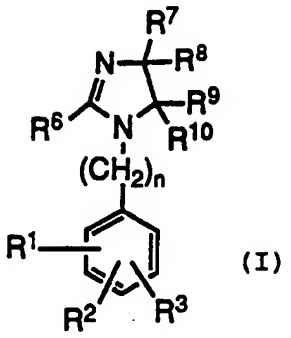
Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise in conjunction with another therapeutic agent. When the drugs are administered in physical combination, the dosage form and administration route should be selected for compatibility with both drugs.

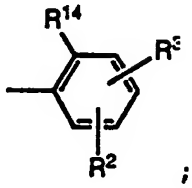
What is claimed is:

1. A compound of formula (I)



(I)

R^1 is other than in the ortho position and is:



;

R^2 is

(a) H,

(b) halo (F, Cl, Br, I),

(c) C_1-C_4 alkyl,

(d) C_1-C_4 alkoxy,

(e) C_1-C_4 acyloxy,

(f) C_1-C_4 alkylthio,

(g) C_1-C_4 alkylsulfinyl,

(h) C_1-C_4 alkylsulfonyl,

(i) hydroxy (C_1-C_4) alkyl,

(j) aryl (C_1-C_4) alkyl,

(k) $-CO_2H$,

(l) -CN,

(m) tetrazol-5-yl,

(n) $-CONHOR^{13}$,

(o) $-SO_2NHR^{23}$,

(p) $-NH_2$,
(q) C_1-C_4 alkylamino,
(r) C_1-C_4 dialkylamino,
(s) $-NHSO_2R^{24}$,
(t) $-NO_2$,
(u) furyl,
(v) aryl;

wherein aryl is phenyl optionally substituted with one or two substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-CF_3$, C_1-C_4 alkylthio, $-OH$, $-NH_2$, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, $-CN$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2$-benzyl;

R^3 is
(a) H,
(b) halo,
(c) C_1-C_4 alkyl,
(d) C_1-C_4 alkoxy,
(e) C_1-C_4 alkoxyalkyl;

R^4 is
(a) $-CN$,
(b) $-NO_2$,
(c) $-CO_2R^{11}$;

R^5 is
(a) H,
(b) C_1-C_6 alkyl,
(c) C_3-C_6 cycloalkyl,
(d) C_2-C_4 alkenyl,
(e) C_2-C_4 alkynyl;

R^6 is
(a) C_1-C_{10} alkyl,
(b) C_3-C_8 alkenyl,
(c) C_3-C_8 alkynyl,
(d) C_3-C_8 cycloalkyl,

(e) C_4-C_8 cycloalkenyl,

(f) C_4-C_{10} cycloalkylalkyl,

(g) C_5-C_{10} cycloalkylalkenyl,

(h) C_5-C_{10} cycloalkylalkynyl,

(i) $-(CH_2)_sZ^2(CH_2)_mR^5$,

(j) phenyl, optionally substituted with 1-2 substituents selected from the group of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, amino, hydroxy and benzyloxy;

(k) benzyl, optionally substituted on the phenyl ring with 1-2 substituents selected from the group of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy or $-NO_2$;

R^7, R^8, R^9, and R^{10} are independently chosen from

(a) H,

(b) C_1-C_8 alkyl unsubstituted or substituted by one or more halogen

(c) C_3-C_6 cycloalkyl

(d) NO_2,

(e) CN,

(f) $CONR^{15}R^{16}$,

(g) CO_2R^{17},

(h) OR^{18},

(i) $(CH_2)_nCONR^{15}R^{16}$ where n is 1-4,

(j) $(CH_2)_nCO_2R^{17}$ where n is 1-4,

(k) $(CH_2)_nOR^{18}$ where n is 1-4,

(l) aryl, wherein aryl is as defined above,

(m) CH_2aryl, wherein aryl is as defined above,

(n) R^9 and R^{10} taken together are $-(CH_2)_nX(CH_2)_m-$,

(o) R^9 and R^{10} taken together are $-(CH_2)_t-$,

(p) R^7 and R^8 taken together can be S, O, NR^{19}, or $CR^{11}R^{12}$,

(q) R^9 and R^{10} taken together can be NR^{19},

(r) R^9 and R^{10} taken together can be S or O provided that R^7 and R^8 independently or when taken together are not C_1-C_8 alkyl unsubstituted or C_1-C_8 alkyl substituted with a substituent selected from the group of halogen, C_3-C_6 cycloalkyl, $(CH_2)_nOR^{18}$, aryl, wherein aryl is as defined above, or $-(CH_2)t-$,

(s) R^7 and R^9 taken together form an imide $-CONR^{22}CO-$,

(t) R^7 and R^9 taken together are $-CH_2NR^{22}CH_2-$, provided that both R^7, R^8 and R^9, R^{10} are not S, O, NR^{19}, or $-(CH_2)t-$,

(u) (3-indolyl) methyl,

(v) (4-imidazolyl) methyl;

R^{11} and R^{12} are independently

(a) H,

(b) C_1-C_6 alkyl,

(c) C_3-C_6 cycloalkyl,

(d) phenyl,

(e) benzyl,

(f) when taken together are $-CH_nXCH_n-$,

R^{13} is

(a) H,

(b) methyl,

(c) benzyl;

R^{14} is

(a) $-CO_2H$,

(b) $-CH_2CO_2H$,

(c) $-C(CF_3)_2OH$,

(d) $-CONHNHSO_2CF_3$,

(e) $-CONHOR^{13}$,

(f) $-CONHSO_2R^{24}$,

(g) $-CONHSO_2NHR^{23}$,

(h) $-C(OH)R^{23}PO_3H_2$,

(i) $-NHCOCF_3$,

(j) $-NHCONHSO_2R^{24}$,

(k) $-NHPO_3H_2$,

(l) $-NHSO_2R^{24}$,

(m) $-NHSO_2NHCOR^{24}$,

(n) $-OPO_3H_2$,

(o) $-OSO_3H$,

(p) $-PO(OH)R^{23}$,

(q) $-PO_3H_2$,

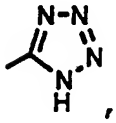
(r) $-SO_3H$,

(s) $-SO_2NHR^{23}$,

(t) $-SO_2NHCOR^{24}$,

(u) $-SO_2NHCONHR^{23}$,

(v)



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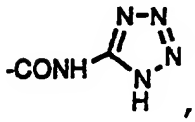
(w)



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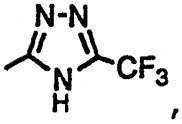
(x)



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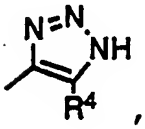
(y)



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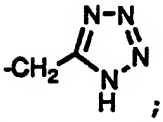
(z)



;

R^{15} and R^{16} are independently

(a) H,

(b) C_1-C_6 alkyl,

(c) aryl, wherein aryl is as defined above,

(d) aryl (C_1-C_4) alkyl, wherein aryl is as defined above,

or taken together constitute a

(e) piperidine ring,

(f) morpholine ring,

(g) piperazine ring, optionally N-substituted with C_1-C_6 alkyl, phenyl or benzyl;

R^{17} is

(a) H,

(b) C_1-C_6 alkyl,

(c) phenyl,

(d) benzyl;

R^{18} is

(a) H,

(b) C_1-C_6 alkyl,

(c) phenyl,

(d) benzyl;

R^{19} is

(a) H,

(b) OR^{18},

(c) C_1-C_6 alkyl,

(d) aryl,

(e) C_1-C_6 alkyl aryl, wherein aryl is as defined above,

(f) $NR^{20}R^{21}$;

R^{20} and R^{21} are independently

(a) H,

(b) C_1-C_6 alkyl,

(c) phenyl,

(d) benzyl,

or taken together constitute a

(e) piperidine ring,

(f) morpholine ring,

(g) piperazine ring, optionally N-substituted with C_1-C_6 alkyl, phenyl or benzyl;

R^{22} is

(a) H,

(b) C_1-C_6 alkyl,

(c) benzyl;

R^{23} is

(a) H,

(b) C_1-C_5 alkyl,

(c) aryl,

(d) $-CH_2$-aryl, where aryl is defined as above,

(e) heteroaryl;

wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted 5- or 6-membered aromatic ring which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N, and S and wherein the substituents are members selected from the group consisting of -OH, -SH, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CF_3$, halo, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CO_2$-benzyl, $-NH_2$, C_1-C_4 alkylamino, or C_1-C_4 dialkylamino;

R^{24} is

(a) aryl, where aryl is as defined above,

(b) C_3-C_7 cycloalkyl,

(c) C_1-C_4 perfluoroalkyl,

(d) C_1-C_4 alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, -SH, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, $-CF_3$, halo, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CO_2$-benzyl, $-NH_2$, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, or $-PO_3H_2$;

(e) heteroaryl awhere heteroacryl is defined above;

X is

(a) S,

(b) O,

(c) $-NR^{22}-$;

Z is

(a) $-O-$,

(b) $-S-$,

(c) $-NR^{11}-$;

m is 1 to 5;

n is 1 to 4;

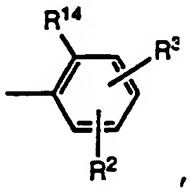
s is 0 to 5;

t is 2 to 5;

or a pharmaceutically acceptable salt thereof.

2. a compound of claim 1 wherein

R^1 is in the para position and is



,

R^6 is

(a) C_1-C_{10} alkyl,unsubstituted or substituted with one or more halogen

(b) C_3-C_{10} alkenyl,

(c) C_3-C_{10} alkynyl,

(d) C_3-C_8 cycloalkyl,

(e) phenyl, optionally substituted with 1-2 substituents selected from the group of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, amino, hydroxy and benzyloxy;

(f) benzyl, optionally substituted on the phenyl ring with one or two substitutents selected from the

group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy and $-NO_2$;

R^7, R^8, R^9, R^{10} are independently

(a) H,

(b) C_1-C_8 alkyl unsubstituted or substituted by one or more halogen

(c) C_3-C_6 cycloalkyl

(d) R^9 and R^{10} taken together are $-(CH_2)_t-$,

(e) R^7 and R^8 taken together can be S, O, NR^{19},

(f) R^9 and R^{10} taken together can be NR^{19}, provided that R^9 and R^{10} cannot be taken together to form NR^{19}, or $-(CH_2)t-$, when R^7 and R^8 are taken together to form S, O, NR^{19},

(g) aryl, wherein aryl is as defined above,

(h) R^9 and R^{10} taken together are $-(CH_2)_nX(CH_2)_m-$,

(i) R^7 and R^8 taken together can be S, O, NR^{19}, $CR^{11}R^{12}$,

(j) R^9 and R^{10} taken together can be or O provided that R^7 and R^8 independently or taken together are not C_1-C_8 alkyl unsubstituted or C_1-C_8 substituted with a substituent selected from the group of more halogen, C_3-C_6 cycloalkyl, $(CH_2)_nOR^{18}$, aryl, wherein aryl is as defined above, or $-(CH_2)_t-$;

R^{14} is

(a) $-CO_2H$,

(b) $-CONHSO_2R^{24}$,

(c) $-NHCONHSO_2R^{24}$,

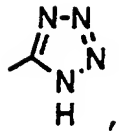
(d) $-NHSO_2R^{24}$,

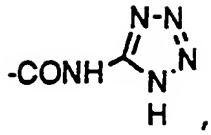
(e) $-PO_3H_2$,

(f) $-SO_3H$,

(g) $-SO_2NHR^{23}$,

(h) $-SO_2NHCONHR^{23}$,

(i)  ,

(j)  ,

(k) $-SO_2NHCOR^{24}$,

(l) $NHSO_2NHCOR^{24}$;

or a pharmaceutically acceptable salt thereof.

3. a compound of claim 2 wherein

R^2 is

(a) H,

(b) halo,

(c) C_1-C_4 alkyl,

(d) C_1-C_4 alkoxy;

R^6 is

(a) C_1-C_7 alkyl,

(b) C_3-C_4 alkenyl,

(c) C_3-C_4 alkynyl;

(d) phenyl, optionally substituted with 1-2 substituents selected from the group of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, amino, hydroxy and benzyloxy;

R^{14} is

(a) $-CO_2H$,

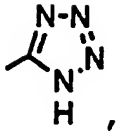
(b) $-CONHSO_2R^{24}$,

(c) $-NHCONHSO_2R^{24}$,

(d) $-NHSO_2R^{24}$,

(e) $-SO_2NHR^{23}$,

(f) $-SO_2NHCONHR^{23}$,

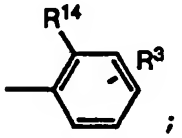
(g)  ,

(h) $NHSO_2NHCOR^{24}$,

(i) SO_2NHCOR^{24};

or a pharmaceutically acceptable salt thereof.

4. a compound of claim 3 wherein

R^1 is  ;

or a pharmaceutically acceptable salt thereof.

5. A compound of claim 4 selected from the group consisting of

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-butyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-butenyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-ditrifluoromethyl-2-propyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dicyclopropyl-2-propyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-butenyl-1-[(2'-(N-((phenylsulfonyl)carboxamido)biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(trifluoromethanesulfonylamido)biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(N-benzoylsulfonamido)biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(N-(4-chloro)benzoylsulfonamido) biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-diazaspiro-((4.5))-deca-3-ene-2-propyl-1-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 3,5-Dihydro-5-(1-phenylethylidene)-2-propyl-3-[(2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(N-hexanoylsulfonamido)biphen-4-yl)methyl]-4H-imidazol-4-one

- 1,5-dihydro-5,5-dimethyl-2-propyl-1-[(2'-(N-trifluoroacetylsulfonamido)biphen-4-yl)methyl]-4H-imidazol-4-one

6. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a compound of any one of Claims 1 through 4.

7. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a compound of Claim 5.

8. A method of treating hypertension in a warm blooded animal comprising administering to an animal in need of such treatment an effective amount of a compound of any of Claims 1 through 4.

9. A method of treating hypertension in a warm blooded animal comprising administering to an animal in need of such treatment an effective amount of a compound of Claim 5.

10. A method of treating congestive heart failure in a warm blooded animal comprising administering to an animal in need of such treatment an effective amount of a compound of any of Claims 1 through 4.

11. A method of treating congestive heart failure in a warm blooded animal comprising administering to an animal in need of such treatment effective of a compound of Claim 5.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/07021

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D233/70; A61K31/415; C07D233/84; C07D233/88
C07D235/02; C07D403/10; C07D403/06; C07D403/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 380 959 (E.I.DU PONT DE NEMOURS AND COMPANY) 8 August 1990 ---	
A	EP,A,0 412 594 (MERCK & CO. INC.) 13 February 1991 ---	
A	EP,A,0 419 048 (MERCK & CO. INC.) 27 March 1991 ---	
A	EP,A,0 291 969 (E.I.DU PONT DE NEMOURS AND COMPANY) 23 November 1988 ---	
P,X	EP,A,0 475 898 (CIBA-GEIGY AG) 18 March 1992 cited in the application see page 2, line 1 - line 31 see page 4, line 5 - line 55 ---	1-2,6-11

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 DECEMBER 1992	23. 12. 92

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	DE BUYSER I.A.F.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	WO,A,9 114 679 (SANOFI) 3 October 1991 cited in the application see page 49, line 12 - page 50, line 2	1,6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/07021

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8-11
because they relate to subject matter not required to be searched by this Authority, namely:
see annex

2. [X] Claims Nos.: 1-4,6,8,10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see annex

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

"Remark: Although claims 8-11 are directed to a method of treatment of (diagnostic method practised on) the human animal body the search has been carried out and based on the alleged effects of the compound/ composition."

Claims not searched: 1-4,6,8,10
As the drafting of the claims is not clear and concise (Art.6,PCT) and encompasses such an enormous amount of products, a complete search is not possible on economic grounds(See Art.17(2)(a)(ii),PCT). Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been based on the examples.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9207021 SA 63822

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 02/12/92

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0380959	08-08-90	US-A-	4916129	10-04-90
		AU-B-	618503	19-12-91
		AU-A-	4854590	26-07-90
		CA-A-	2006604	19-07-90
		JP-A-	3002169	08-01-91
EP-A-0412594	13-02-91	CA-A-	2021954	29-01-91
		JP-A-	3148266	25-06-91
EP-A-0419048	27-03-91	US-A-	5100897	31-03-92
		CA-A-	2024113	01-03-91
		JP-A-	3197466	28-08-91
EP-A-0291969	23-11-88	US-A-	4820843	11-04-89
		AU-B-	603525	15-11-90
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		JP-A-	1117876	10-05-89
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		US-A-	4874867	17-10-89
EP-A-0475898	18-03-92	AU-A-	8375591	12-03-92
		CA-A-	2050769	11-03-92
WO-A-9114679	03-10-91	FR-A-	2659967	27-09-91
		FR-A-	2665702	14-02-92
		AU-A-	7561091	21-10-91
		CA-A-	2057913	21-09-91
		EP-A-	0454511	30-10-91